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Modular Approach to the Bisbenzylisoquinoline Alkaloids Tetrandrine and Isotetrandrine and Synthesis of Novel Analogues

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Erklärung

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Eidesstattliche Versicherung

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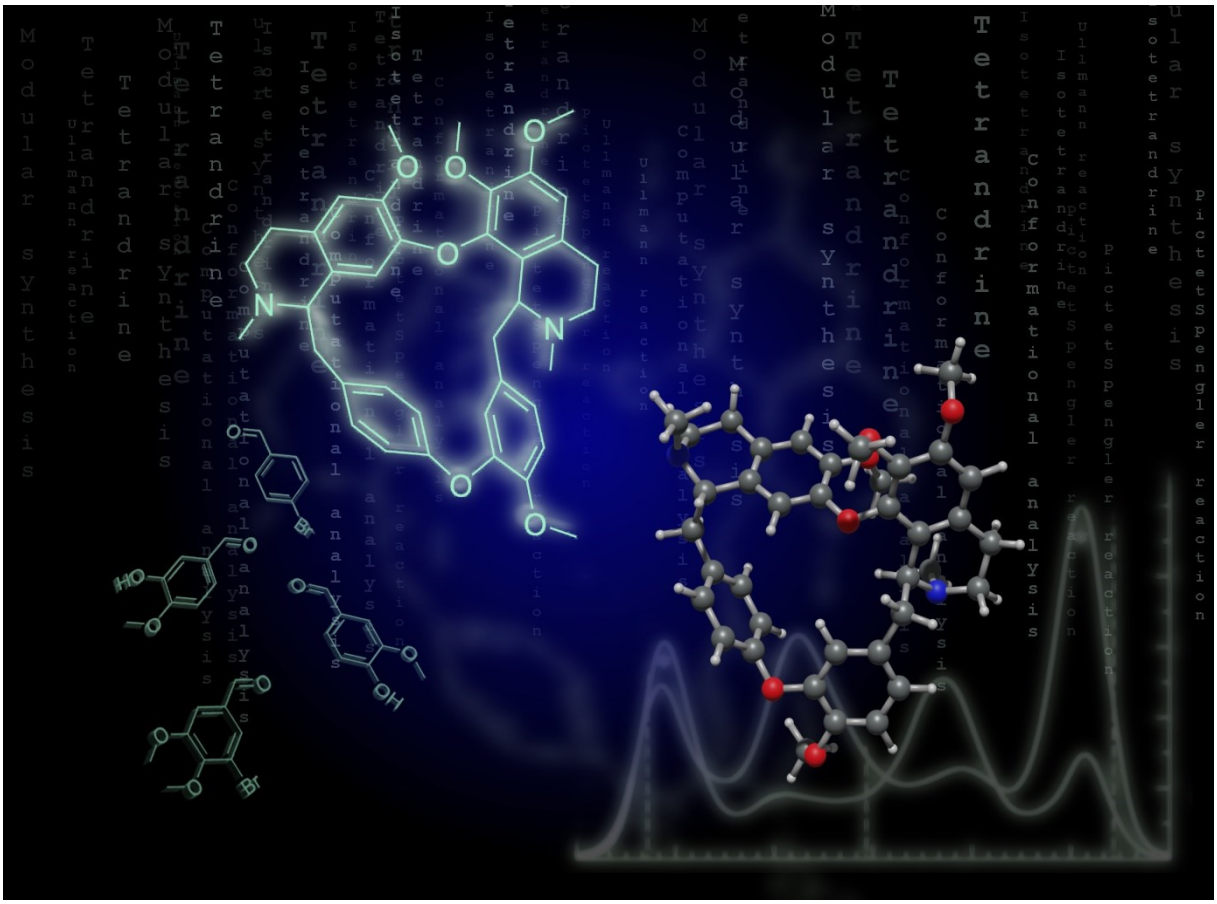

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PUBLICATIONS

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R. Schütz, S. Schmidt, F. Bracher: A versatile approach to 1-oxo-, 1-oxo-3,4-dihydro- and 1,3,4-trioxo isoquinoline alkaloids and first total synthesis of the dimeric 1-oxoisoquinoline alkaloids berbanine and berbidine, *Tetrahedron*, **2020**, 76, 131150.

R. Schütz, M. Müller, S. Gerndt, K. Bartel, F. Bracher: Racemic total synthesis and evaluation of the biological activities of the isoquinoline–benzylisoquinoline alkaloid muraricine. *Arch. Pharm.*, **2020**, 353, e2000106.

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1 INTRODUCTION

The natural product tetrandrine (**1**, Figure **1**) belongs to the class of bisbenzylisoquinoline alkaloids, which can be mainly found in the plant families Menispermaceae, Berberidaceae, Lauraceae, and Ranunculaceae[2-3].

Tetrandrine (**1**) was first isolated by Kondo and Yano in 1928[4-5] from the climbing plant *Stephania tetrandra S. Moore* (Menispermaceae). The root of this herb has been used in Chinese and Japanese traditional medicine for treating diverse diseases such as tuberculosis, malaria, asthma, hyperglycemia, hypertension and cancer[6]. Apart from the traditional use the pharmacological effects of tetrandrine (**1**) in its isolated form have been extensively studied. In this work anticancer, antiviral, chemoresistance reversing and calcium channel blocking activities will be emphasized and discussed in the following.

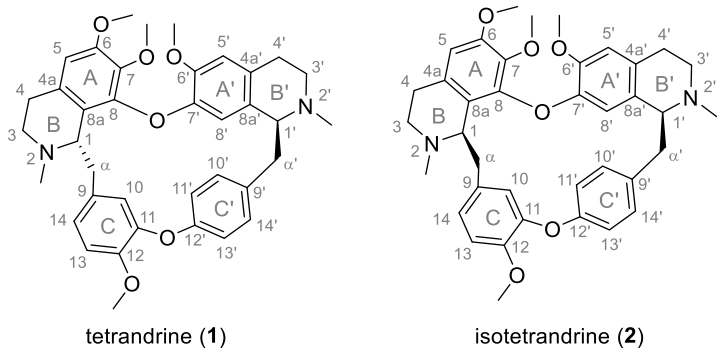


Figure 1. Tetrandrine (**1**) (1*S*,1'*S*) and isotetrandrine (**2**) (1*R*,1'*S*) – Numbering of the skeleton according to the convention established by Shamma[7] (Reproduced from ref. 1 by permission from The Royal Society of Chemistry).

Also for the isomer isotetrandrine (**2**, Figure **1**) biological activities such as anticancer[8-10], multidrug resistance reversing[11-12], antioxidative[13] and autoimmune disease modifying[14] effects are reported.

1.1 BISBENZYLISOQUINOLINE ALKALOIDS – AN OVERVIEW

As the name suggests, bisbenzylisoquinolines consist of two benzylisoquinoline moieties. The isoquinoline is mostly saturated to a tetrahydroisoquinoline, but also partially reduced dihydroisoquinolines and fully aromatic isoquinoline moieties can be found in natural products. Depending on the degree of saturation up to two asymmetric centres (C-1 and C-1') are present. Bisbenzylisoquinolines appear as macrocyclic dimers or in their open chained *seco*-form. The monomers are linked through one or more diaryl ether bridges, biphenyl bridges, phenyl-benzyl ether bridges or a combination thereof. The monomers can be connected in different orientations regarding the isoquinoline unit (referred as “head”) and the benzyl unit

(referred as “tail”), resulting in three possible connection patterns “head-to-head”, “head-to-tail” and “tail-to-tail”. The diversity of bisbenzylisoquinolines is represented by selected examples of some subtypes in Figure **2**. Tetrandrine (**1**) is linked by a “head-to-head” and “tail-to-tail” bridge according to this classification. Common substituents of bisbenzylisoquinolines in the aromatic moiety are hydroxy, methoxy and methylenedioxy groups.

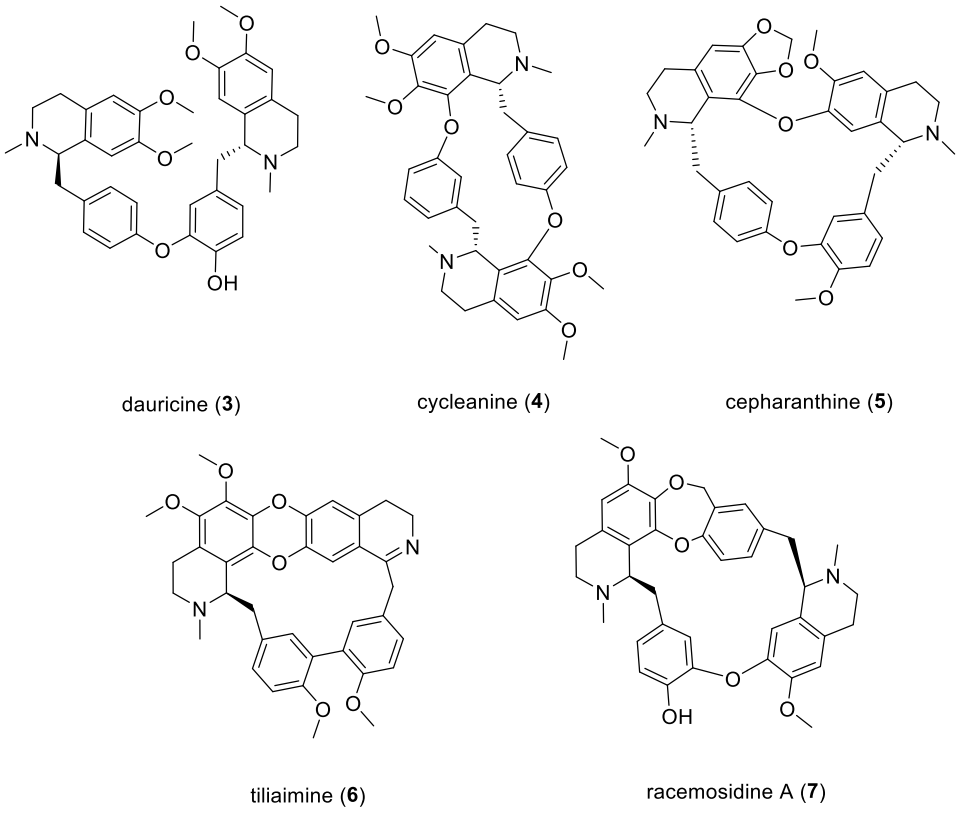


Figure 2. *Seco*-bisbenzylisoquinoline dauricine (**3**) and macrocyclic bisbenzylisoquinolines cycleanine (**4**), cepharanthine (**5**), tiliaimine (**6**) and racemosidine A (**7**).

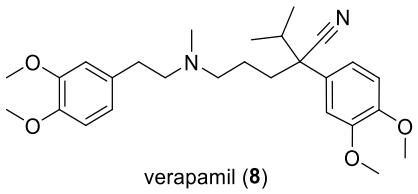
1.2 BIOLOGICAL ACTIVITIES OF TETRANDRINE (1)

As already mentioned multiple biological activities have been reported for tetrandrine (**1**). In the following part its anticancer, antiviral, chemoresistance reversing and calcium channel blocking activities will be emphasized.

1.2.1 TETRANDRINE (1) AS CA^{2+} CHANNEL BLOCKER

A study in 1982[15] found that tetrandrine (**1**) is a modulator of Ca^{2+} channels that blocks in a similar manner as verapamil (**8**, Figure **3**), a blocker of voltage-dependent L-type Ca_v channels.

Further studies confirmed inhibitory effects of tetrandrine (**1**) on L-type Ca_v channels[16-18] and identified also T-type Ca^{2+} channels as pharmacological target[19-20].



verapamil (**8**)

Figure 3. Structure of verapamil (**8**), a blocker of L-type calcium channels.

Moreover tetrandrine (**1**) was found as a blocker of two-pore channels (TPCs)[21], which are also members of the superfamily of voltage-gated calcium channels[22]. TPCs are located on the membranes of endolysosomes[3, 22-23], which are intracellular acidic calcium stores that are important organelles for the endocytotic transport in cells[3, 22, 24] and therefore vital for physiological functions in the cell. TPCs are an interesting pharmacological target since they play a key role in the pathomechanism of diseases such as cancer[25] and viral infections[21], which will be discussed in detail in the following.

1.2.2 ANTIVIRAL ACTIVITY

Recent studies have shown that tetrandrine (**1**) possesses antiviral properties against Ebola virus (EBOV)[21, 26] and the coronaviruses MERS-CoV[27] and SARS-CoV-2[28]. Hereby tetrandrine (**1**) reduced the infectivity by affecting a late entry step of the viruses (or pseudoviruses respectively that served as model viruses) into host cells. These studies suggest tetrandrine's (**1**) TPC blocking property to be the mode of action. The infection pathways of these viruses are similar, with TPCs being a vital host cell factor. After binding of the virus to cell surface receptors it is internalized through endocytosis to facilitate host cell entry. The virus is then translocated *via* the endolysosomal system before the virus core is released to the cell cytoplasma where it replicates. Since TPCs are important players in the regulation of endolysosomal trafficking, these channels are a potential target for pharmacological intervention.

Sakurai *et al*. could halt EBOV infection *in vitro* in human monocyte-derived macrophages with tetrandrine (**1**) in submicromolar concentrations (IC_{50} = 55 nM)[21]. In further *in vivo* studies the treatment of infected mice with tetrandrine (**1**) significantly enhanced the survival rate.

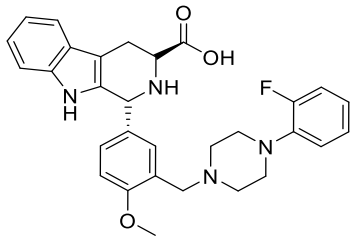
Another study investigated the inhibitory effect of several bisbenzylisoquinoline alkaloids on MERS-CoV infectivity *in vitro*[27]. Among several tested bisbenzylisoquinolines and a series of known ion channel modulators, tetrandrine (**1**) was one of the most potent inhibitors of MERS-CoV pseudovirus infectivity with an IC_{50} of 7.0 µM.

Also against the novel coronavirus SARS-CoV-2 tetrandrine (**1**) showed antiviral activity *in vitro*[28]. The TPC-mediated virus entry could be decreased by blocking the TPC activity. Currently, in China a clinical trial (NCT04308317)[29] is announced to investigate orally administered tetrandrine (**1**) as adjuvant treatment of COVID-19 patients. It needs to be stated that although this study is officially registered on clinicaltrails.gov, a database provided by the U.S. National Library of Medicine, it has to be seen critically. The study is registered as a phase 4 study, despite this late stage of the approval process is impossible considering the novelty of the disease intended to treat. However, it is worth to observe the progress and the possible outcome of this study.

1.2.3 ANTICANCER ACTIVITY

The effect of tetrandrine (**1**) on different types of cancer has been extensively investigated[30]. As antitumor agent the alkaloid may not have one specific target but several. It modulates diverse physiological functions of cancer cells and therefore intervenes in multiple aspects of oncogenesis. It was found to affect the proliferation[31], angiogenesis[32], migration[25], apoptosis[33-34] and chemoresistance of tumors[35]. TPCs[25], cell cycle regulating kinases[36-37], apoptosis inducing caspases[38], tumor suppressor genes[37], death receptors and efflux pumps[39-42] are discussed targets to be modulated by tetrandrine (**1**)[35]. In the following the role of TPCs and efflux pumps in cancer will be outlined.

Recently it was shown that TPCs are an important factor for the migration, angiogenesis and growth of tumors[25, 43-44]. As mentioned before, TPCs are located on the membranes of endolysosomes[3, 22-23] and thereby regulate multiple functions in cancer cells, such as the trafficking and recycling of integrins[45]. Integrins are transmembrane receptors that facilitate the adhesion and migration of tumor cells. By the pharmacological inhibiton of TPCs with tetrandrine (**1**) or Ned-19[44] (**9**, Figure **4**), both known blockers of TPCs, the migration and vascularization of tumor cells could be impaired *in vitro* and *in vivo*[25]. It was further shown that TPCs mediate vascular endothelial growth factor (VEGF)-induced neoangiogenesis[46]. Through a blockade of TPCs the VEGF-induced formation of new blood vessels could be inhibited[47]. This data reveals the role of TPCs in cancer and identifies these cation channels as a pharmacological target for tumor therapy.



Ned-19 (**9**)

Figure 4. Structure of Ned-19 (**9**), a blocker of TPC channels.

1.2.4 TETRANDRINE (1) AS A REVERSER OF MULTIDRUG RESISTANCE

Apart from a direct anticancer activity tetrandrine (**1**) showed synergistic effects on resistant cancer cell lines in combination with other common antitumor agents such as vincristine, doxorubicine and paclitaxel. Hereby tetrandrine (**1**) was able to resensitize chemoresistant tumors by levering the resistance mechanism. As the mode of action several studies discuss the modulation of P-glycoprotein (P-gp)[39, 41-42, 48-49] either by downregulation or by direct inhibition. P-gp is a universal efflux pump for xenobiotics, which is a key factor of drug resistance[50] causing treatment failure of tumor therapy. The multidrug resistance-associated protein 1 (MRP1), another unspecific transporter protein, was also reported as a target of tetrandrine (**1**)[40]. By suppressing the P-gp/MRP1-mediated efflux of chemotherapeutic drugs, the intracellular accumulation increases and the anticancer effect is restored consequently. Under the name CBT-1™ tetrandrine (**1**) is investigated in clinical studies[51-52] (NCT03002805/ NCT00972205/ NCT00437749) and intended for the therapy of multidrug resistant tumors.

1.2.5 TOXICITY OF TETRANDRINE (1)

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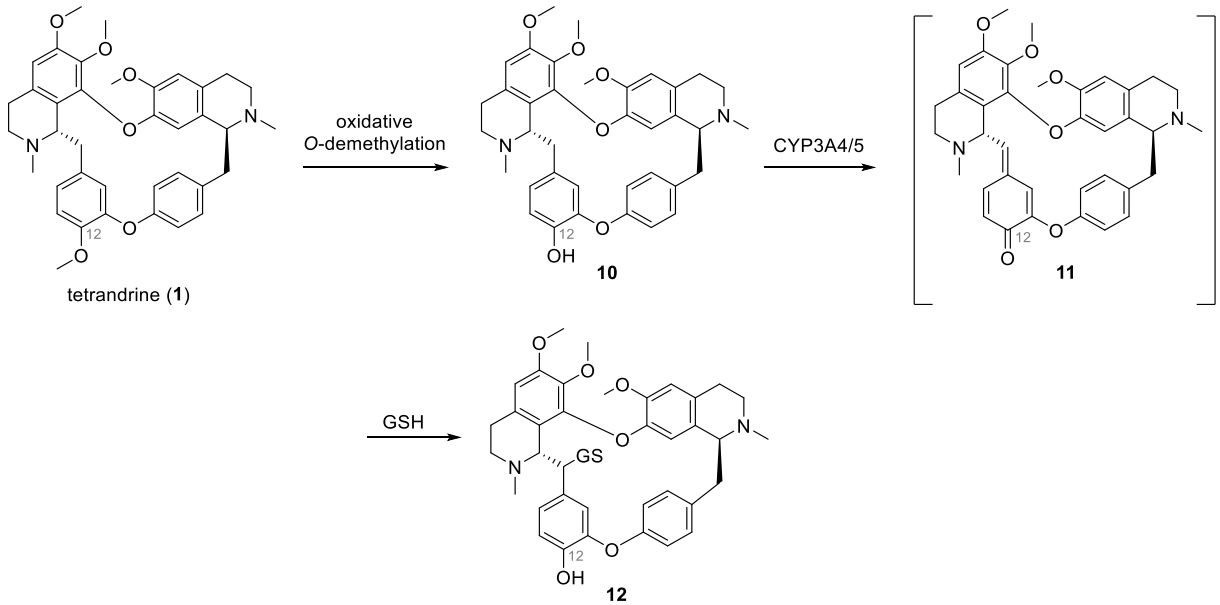
Despite its versatile pharmacological effects the clinical use of tetrandrine (**1**) as a drug is limited by its toxicity. Several toxic side effects have been reported for tetrandrine (**1**) and other bisbenzylisoquinolines so far[54]. In animal models mainly an injury of liver and lung was observed[55-58].

The molecular mechanism of tetrandrine-induced toxicity has not been entirely elucidated yet. Li and coworkers[59] hypothesized that an interaction of tetrandrine (**1**) with p38α MAPK (mitogen-activated protein kinase) led to liver injury, whereas several other studies suggest the involvement of cytochrome P450 (CYP) enzymes in tetrandrine-induced pulmonary[55-56] and hepatic toxicity[60]. Qi *et al*.[60] considered CYP2E1 as primary reason for mitochondrial

dysfunction of rat hepatocytes after tetrandrine (**1**) exposure, which they related to reactive oxygen species (ROS) that were generated in the course of CYP2E1 metabolism. However, it is unknown which molecular mechanisms are connected to CYP2E1-mediated toxicity. In a metabolic study by Jin *et al*.[55] a CYP3A4- and CYP3A5-mediated metabolism equally leading to a potentially toxic intermediate is described. Hereby one particular structural element is suggested to be responsible for tetrandrine's (**1**) toxicity. In the hypothesized metabolic pathway, the methoxy group at C-12 in *para*-position to a benzylic methylene group is first demethylated to give the corresponding phenol **10**. This phenol then undergoes enzymatic oxidation to the *para*-quinone methide **11**, which is an electrophilic intermediate prone to attack bio-nucleophiles (see Scheme **1**). After incubation of tetrandrine (**1**) with human liver mircosomes in the presence of glutathione (GSH), a corresponding GSH conjugate (**12**) was detected *via* LC-MS, which provides evidence for the formation of the *para*-quinone methide **11**.



Scheme 1. CYP-enzyme mediated oxidative metabolism of tetrandrine (**1**) adopted from Jin *et al*[55].

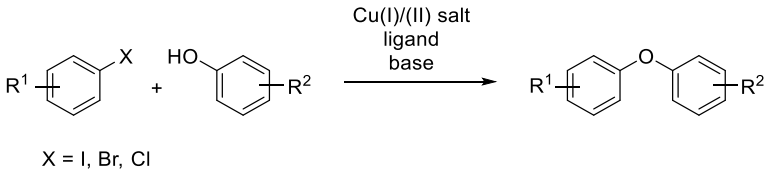
1.3 SYNTHETIC APPROACHES

Central structural motifs in the bisbenzylisoquinoline scaffold are the diaryl ether and the tetrahydroisoquinoline moiety. For the construction of both moieties a number of methods is available. In the following a concise overview focusing on the most prominent methods is provided. Furthermore protocols of already published syntheses of tetrandrine (**1**) and derivatives will be discussed briefly.

1.3.1 SYNTHESIS OF DIARYL ETHERS

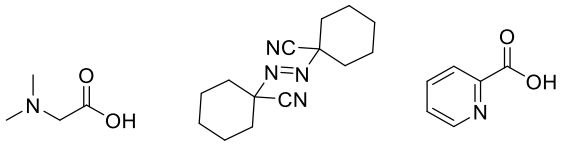
1.3.1.1 ULLMANN REACTION

The Ullmann-type cross-coupling is the most commonly utilized method for the construction of diaryl ethers in the synthesis of natural products[61]. Fritz Ullmann originally invented this method in the 20th century reacting aryl halides in the presence of copper to form biaryl compounds[62]. He extended this approach to the preparation of diarylamines[63] and diaryl ethers[64]. In his first successful attempt in the construction of diaryl ethers aryl halides were reacted with phenols in the presence of KOH or elementary potassium, respectively, and neat copper at elevated temperatures (> 200 °C)[64]. Harsh reaction conditions (high temperatures and strong bases), high catalytist loads and restricted substrate scope limit the application of the "classical" Ullmann reactions. To overcome these drawbacks modified protocols for copper-catalyzed cross-coupling reactions employing different copper salts, ligands and weaker bases were explored[65-66].



Scheme 2. Ullman-type cross-coupling reaction of aryl halides and phenols catalyzed by copper/ligand systems.

The use of auxiliary ligands, which are mostly bidentate, enhances the solubility and stability of copper complexes resulting in higher reaction rates, whereas catalyst loadings and reaction temperatures could be reduced[67]. Figure **5** displays examples of ligands, which were tested for the construction of the diaryl ether bridges in the synthesis of tetrandrine (**1**) (see chapter **3.1**).

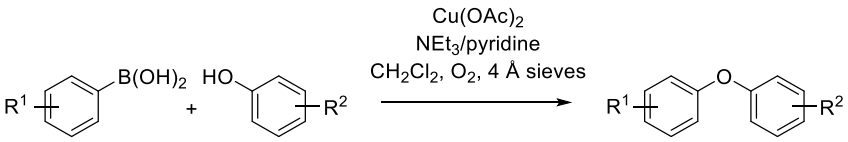


13 14 15

Figure 5. Tested ligands for the Ullmann-type cross-coupling reaction in the synthesis of tetrandrine (**1**) (see Table **2** in chapter **3.1**: *N*,*N*-dimethylglycine[68] (**13**), 1,1'-azo*bis*(cyclohexanecarbonitrile)[69] (**14**) and picolinic acid[70] (**15**)).

1.3.1.2 CHAN-EVANS-LAM COUPLING

Not only aryl halides are suitable for the synthesis of diaryl ethers, but also aryl boronic acids can be utilized as coupling partners. The cross-coupling of aryl boronic acids and phenols (as well as other nucleophiles) was reported by Chan[71] and Evans[72] in 1998. In this approach $Cu(OAc)_2$ is used as catalyst in the presence of the amine bases triethylamine or pyridine furnishing the desired coupling product already at ambient temperature. To prevent competitive side reactions presumably due to the formation of water, the addition of molecular sieves (4 Å) is reported[72].

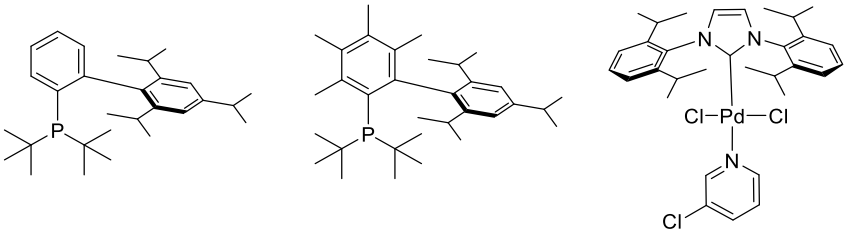


Scheme 3. Chan-Evans-Lam cross-coupling reaction of aryl boronic acids and phenols catalyzed by copper(II)acetate.

Furthermore it was observed that the reaction is performed best under oxygen or ambient atmosphere instead of an inert argon atmosphere[72], which makes this method very convenient.

1.3.1.3 BUCHWALD-HARTWIG CROSS-COUPLING

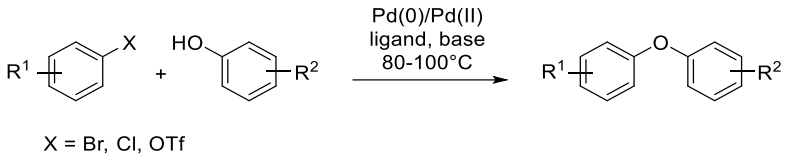
In this transition metal-mediated synthesis of diaryl ethers reported by Buchwald[73] and Hartwig[74] the C–O bond is formed under palladium catalysis at elevated temperatures around 100 °C. In addition electron-rich, sterically bulky phosphine ligands are used as part of the catalytic system. Figure **6** displays the ligands, which were tested for the diaryl ether synthesis in tetrandrine (**1**) (see chapter **3.1**).



16 17 18

Figure 6. Typical ligands or catalysts respectively, used for Buchwald-Hartwig coupling: tBuXPhos (**16**), Me4tButylXphos (**17**) and catalyst PEPPSI™-IPr (**18**), which were tested for the diaryl ether synthesis in tetrandrine (**1**) (see Table **2** in chapter **3.1**).

Mostly $Pd_2(dba)_3$/$Pd(dba)_2$ or $Pd(OAc)_2$ are used as palladium source and K_3PO_4 as base was found to be effective for diaryl ether formation[73]. Scheme **4** shows typical conditions for Buchwald-Hartwig cross-coupling reactions.



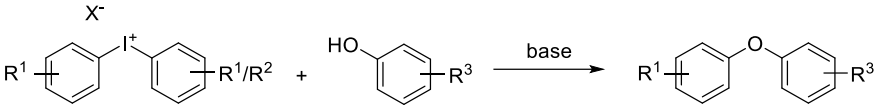
Scheme 4. Buchwald-Hartwig reaction of aryl halides/triflates and phenols catalyzed by a palladium/ligand system.

With this method not only electron-deficient or electronically neutral but also electron-rich aryl halides and aryl triflates readily reacted with a variety of phenols to the corresponding diaryl ethers[73]. Drawbacks of this method are the complex ligands, which are often expensive or not commercially available at all.

1.3.1.4 *O*-ARYLATION WITH DIARYLIODONIUM SALTS

In this attempt hypervalent iodine(III) compounds in the form of diaryliodonium salts are used as arylating agents. In the presence of inorganic bases diaryliodonium salts react with phenols to diaryl ethers at temperatures ranging from ambient temperature to around 100 °C [75-76]. The diaryliodonium salts can be prepared by oxidation of either two iodoarenes or elemental iodine and two arenes or an aryl iodide and an arene with potassium peroxodisulfate ($K_2S_2O_8$) or *m*-chloroperoxybenzoic acid (*m*CPBA) in the presence of strong acids such as TFA or TfOH[77-80]. This method results in either symmetrical or unsymmetrical diaryliodonium salts, which can both be used for arylation. In case of symmetric salts only one aryl group can be transferred to the nucleophile, although this results in the waste of one iodoarene in consequence. Unsymmetric salts consist of one aryl group, which is supposed to be transferred and one auxiliary arene, which serves as “dummy group”[80]. Depending on electronic and steric effects one aryl group is preferably transferred to the nucleophile in the reductive elimination step.

Electron deficient aryl groups are favoured over electron rich arenes, also aryl groups bearing *ortho*-substituents promote reductive elimination[81].



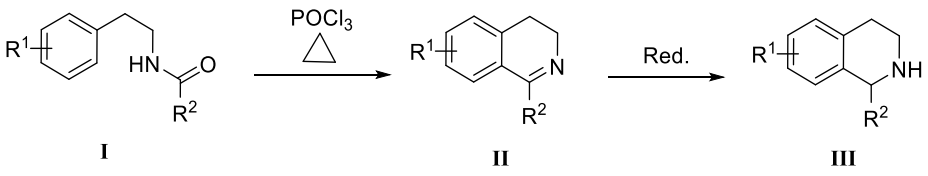
Scheme 5. Diaryl ether synthesis with diaryliodonium salts and phenols (some typical counter ions of the diaryliodonium are X = $^{-}$OTf, $^{-}$OTs, BF_4^-). R^2 = dummy group.

Considering the fact that the aromatic rings in the target compound tetrandrine (**1**) are highly substituted and mostly electron rich due to the presence of methoxy groups, it might be difficult to control the selectivity in the transfer process. This method also requires the synthesis of a suitable diaryliodonium salt in the first step, which makes this approach not the method of first choice.

1.3.2 SYNTHESES OF THE TETRAHYDOISOQUINOLINE MOIETY

1.3.2.1 BISCHLER-NAPIERALSKI REACTION

The Bischler-Napieralski reaction, discovered in 1893 by the eponymous chemists[82], is a commonly used method for the construction of the 1,2,3,4-tetrahydroisoquinoline scaffold in several steps. The first step is the *intra*molecular cyclization of an *N*-acylated *β*-phenethylamine (**I**) typically catalyzed by a lewis acid furnishing a 3,4-dihydroisoquinoline (**II**), followed by the reduction to the corresponding tetrahydroisoquinoline (**III**) in a second step. As diverse natural (bis)benzylisoquinolines are *N*-methylated, a subsequent *N*-methylation is typically an additional step.

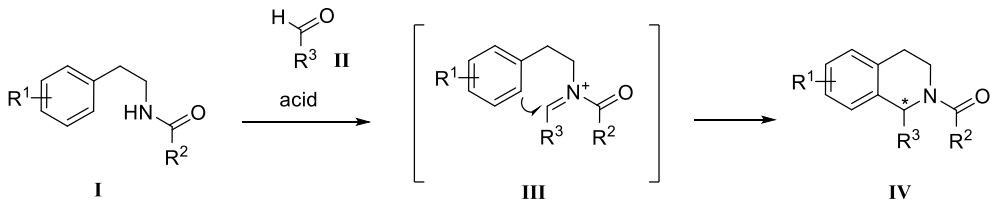


Scheme 6. Typical conditions for the Bischler-Napieralski reaction and subsequent reduction of the resulting 3,4-dihydroisoquinoline **II** to a 1,2,3,4-tetrahydoisoquinoline **III**.

To first access an appropriate amide in this approach, a phenethylamine and an arylacetic acid are required, which are then condensed to the corresponding amide. These arylacetic acid precursors are often difficult to access. Another disadvantage of this method is the comparatively long sequence of steps.

1.3.2.2 PICTET-SPENGLER REACTION

The Pictet-Spengler reaction[83] is a convenient method for the construction of tetrahydroisoquinolines in a one-pot process, typically employing *β*-phenethylamines and aldehydes. Hereby the amine condenses with the aldehyde to form an imine, which then undergoes an *intra*molecular cyclization in the presence of an acid. This method mostly requires phenethylamines bearing electron donating groups, strong acids[84] and elevated temperatures. In the *N*-acyl Pictet-Spengler reaction as a variant, acylated amine precursors (**I**) are used instead that react with aldehydes (**II**) resulting in *N*-acyl iminium intermediates (**III**), which are excellent electrophiles generally enhancing the cyclization reaction[85]. In a nucleophilic attack by the aromatic ring the cyclization takes place under the simultaneous formation of the asymmetric centre at C-1 furnishing the *N*-acyl 1,2,3,4-tetrahydroisoquinolines (**IV**).



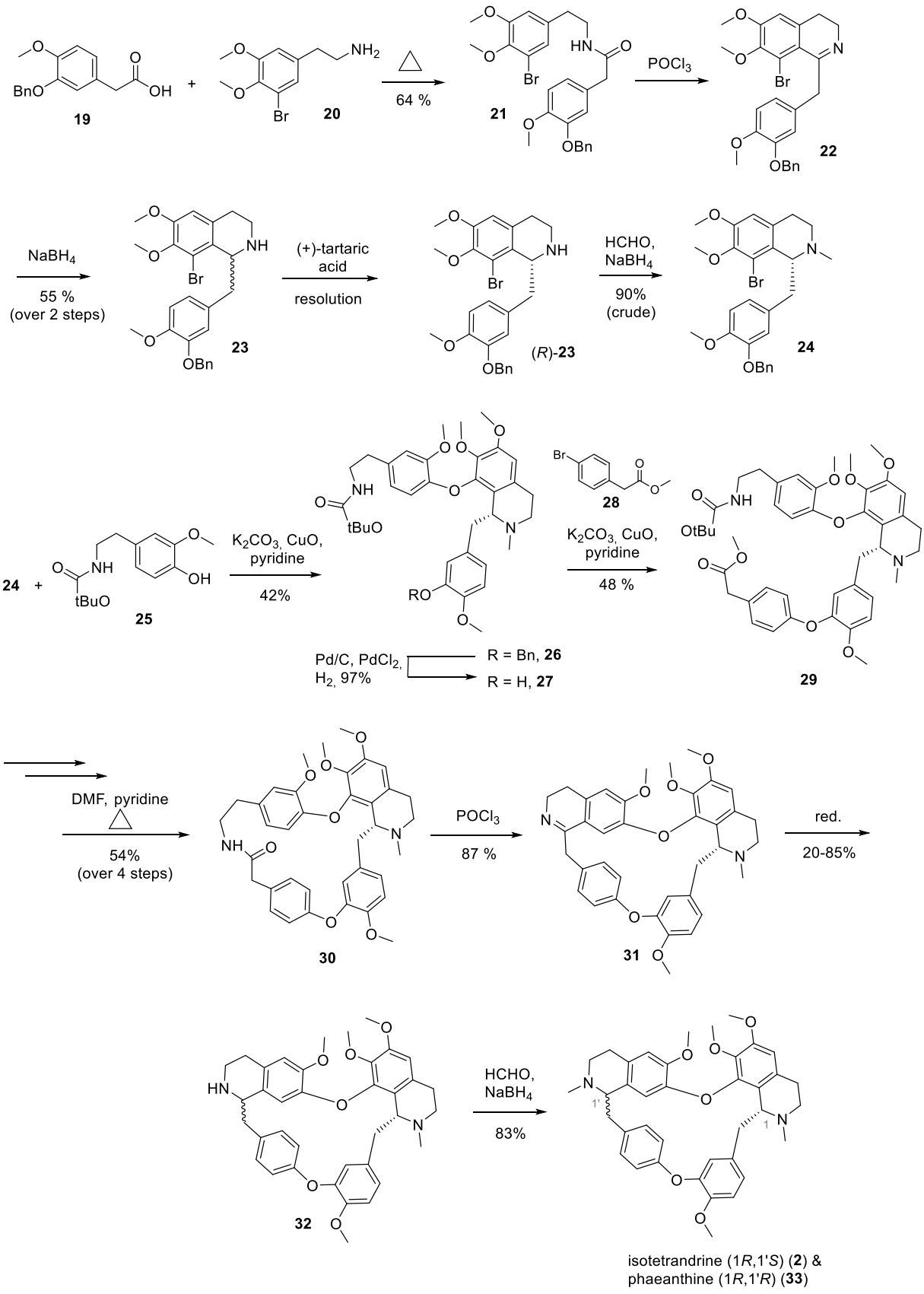
Scheme 7. The *N*-acyl Pictet-Spengler reaction. The aldehyde **II** and *N*-acylated phenethylamine **I** condense to the *N*-acyliminium intermediate **III**, which then undergoes cyclization in a nucleophilic attack by the aromatic ring to give *N*-acylated 1,2,3,4-tetrahydroisoquinoline **IV**.

For the Pictet-Spengler reaction the electrophilic component is not limited to aldehydes, also surrogates like acetals[86-87], enamines[88-89], alkynes[90-91] and enol ethers[92] for example can be employed[93]. Such masked aldehydes are often more stable than arylacetaldehydes, which would be required for the construction of benzyltetrahydroisoquinolines. The high diversity of starting material as well as the access of the tetrahydroisoquinoline moiety in only one step makes this approach very attractive and will be object of preliminary investigations in the following.

1.3.3 PUBLISHED SYNTHESES OF TETRANDRINE (1) AND DERIVATIVES

So far only two synthetic approaches[94-95] to tetrandrine (**1**) are published apart from the synthesis reported in this thesis. In 1968 Inubushi and coworkers accomplished the first total synthesis of tetrandrine (**1**), its enantiomer phaeanthine (**33**) and its diastereomer isotetrandrine (**2**) [94, 96] in more than 20 steps. Central steps in this approach are two copper-catalyzed Ullmann couplings for the construction of the diaryl ether moieties and two Bischler-Napieralski reactions for the formation of the two benzylisoquinoline units. On Scheme **8** the

essential steps of Inubushi's approach are summarized. Aryl acetic acid **19** was condensed with phenethylamine **20** to the amide **21** in a yield of 64%, which was then cyclized in a first Bischler-Napieralski reaction using $POCl_3$. The resulting dihydroisoquinoline **22** was reduced to the racemic tetrahydroisoquinoline **23**, which was converted into its (+)-tartaric acid salt and resolved into the enantiomers *via* fractional crystallization. The isolated free base (*R*)-**23**, which is the precursor for phaeanthine (**33**) or isotetrandrine (**2**) respectively, was subsequently *N*-methylated by reductive alkylation. The (*S*)-isomer of **23** represents the corresponding precursor for the synthesis of tetrandrine (**1**). Next, the *N*-methylated building block **24** was further reacted *via* Ullmann coupling catalyzed by CuO with phenol **25** to give the diaryl ether **26** in 42% yield. After the debenzylation of **26** the obtained phenol **27** was then coupled in a second Ullmann synthesis with methyl *p*-bromophenylacetate **28** to yield the diaryl ether **29**. In a sequence of several steps, which involves the conversion of the methyl ester into a *p*-nitrophenyl ester and the deprotection of the *N*-Boc group, the cyclic amide **30** was obtained in a yield of 54% over 4 steps. Amide **30** was then reacted in an *intra*molecular Bischler-Napieralski cyclization to the 3,4-dihydroisoquinole **31**, which was subsequently reduced to the tetrahydroisoquinoline **32** using different methods, either by Pt-catalyzed hydrogenation, by hydride transfer using $NaBH_4$ or by reduction with Zn/H_2SO_4. By hydride transfer and the reduction with zinc, stereocontrol was achieved to some extent in this step, whereas no stereocontrol was observed in the catalytic hydrogenation resulting in a mixture of diastereomers. Final step was the *N*-methylation of intermediate **32** furnishing (iso)tetrandrine and the corresponding enantiomers, depending on which isomer of intermediate **23** was reacted after resolution. The overall yield in this approach amounts 2.1% (after the combination of the building blocks **19**, **20**, **25** and **28**).



Scheme 8. First published total synthesis of (iso)tetrandrine (**1**/**2**) and phaeanthine (**33**) by Inubushi *et al.*[94]. The synthesis of tetrandrine (**1**) is not explicitly shown, but follows the same synthetic route using the corresponding (*S*)-enantiomer of intermediate **23**.

A very similar approach was recently published in a Chinese patent[95] using the same key reactions. Two racemic benzyltetrahydroisoquinoline units, which were synthesized *via* Bischler-Napieralski cyclization using arylacetic acid and phenethylamine building blocks, were connected in two consecutive Ullmann couplings as the final steps. Consequently, and in contrast to Inubushi's approach, this approach lacks stereoselectivity.

Beside the total synthesis of the natural product a number of semi-synthetic tetrandrine derivatives and the syntheses hereto are published. Hereby the isolated alkaloid from plant sources served as starting material and structural modifications were mainly introduced on C-5 (e.g. (hetero)aryl[97-99] and alkynyl rests[99]) and C-14 (e.g. sulfonamide[100] and (thio)urea[101-102] derivatives) by electrophilic substitution reactions on the electron-rich aromatic rings. Furthermore quaternary ammonium salts[103] of tetrandrine (**1**) are published, which were obtained *via N*-alkylation at N-2'.

2 OBJECTIVES

2.1 AIM OF THIS THESIS

Aim of this work is to develop a new synthetic route to tetrandrine (**1**) and isotetrandrine (**2**), which is more efficient than previously published approaches not only in terms of yield but primarily regarding the total number of steps. The protocol should allow to employ easily accessible building blocks ideally deriving from cheap commercially available starting materials. The synthetic route should allow to flexibly implement diverse structure variations in particular on the aromatic rings. Several routes are to be established, one starting with the construction of rings A-C that are comprising one half of the target molecule and the second one starting with rings A'-C', so that - depending on which aromatic ring is subjected to systematic structure variations - the corresponding modified building block can be inserted in a late stage of the synthesis. Eventhough the synthesis is planned as a racemic approach in the first place, a perspective for controlling the stereochemical outcome *via* asymmetric induction should be provided in a further approach, as high diastereoselectivity of the protocol is aimed for. For this purpose an additional variation of each route should be designed, resulting in a total of four different routes.

Once a synthetic route is established, structure variations of the aromatic ring C are intended. Since the metabolically labile methoxy group at C-12 in ring C is discussed to be responsible for tetrandrine's (**1**) toxicity as already mentioned, an elimination or replacement by different functional groups is targeted. Furthermore, the synthesis of *seco*-analogues based on intermediates of the tetrandrine route is envisaged, as the design of less complex and therefore easier accessible benzylisoquinoline compounds with high biological activity is intended. Eventually all obtained analogues are subject of pharmacological evaluation focussing on anticancer and multidrug resistance reversing activity as well as their toxicity profile.

As an additional synthetic challenge, the total synthesis of three more natural products, namely the isoquinoline alkaloids muraricine (in its racemic form *rac*-**34**), berbanine (**35**) and berbidine (**36**) is to be accomplished.

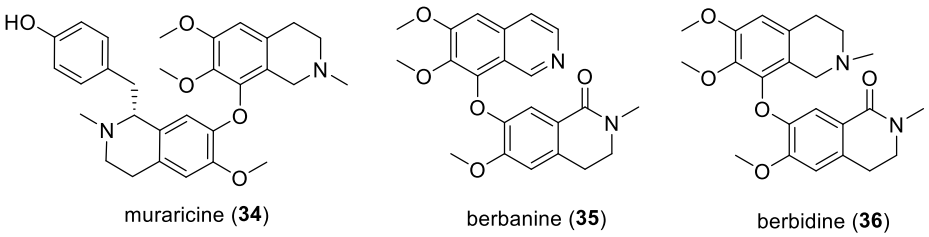


Figure 7. Isoquinoline-benzylisoquinoline alkaloid muraricine (**34**) and isoquinoline-isoquinolone alkaloids berbanine (**35**) and berbidine (**36**).

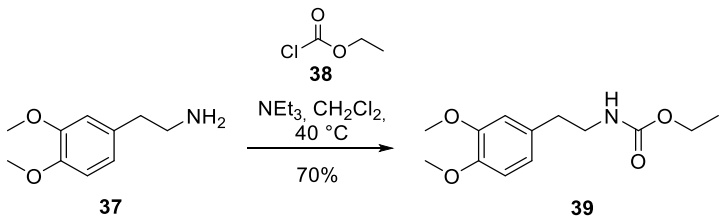
2.2 STRATEGY OF SYNTHESIS

2.2.1 PRELIMINARY STUDIES FOR THE SYNTHESIS OF THE TETRAHYDROISOQUINOLINE SCAFFOLD

In a first step a suitable method for the construction of the tetrahydroisoquinoline moiety is to be selected. Due to the fast access of this structural motif *via* Pictet-Spengler reaction in only one step and the high flexibility of starting material, this method seems very promising for the synthesis of the targeted natural products. It was decided to focus on *N*-acyl Pictet-Spengler condensation, since *N*-acyl iminium intermediates as strong electrophiles readily undergo the cyclization step as discussed before. Carbamates were chosen as acylated phenethylamine building blocks, since they are easily available by treating phenethylamines with acylating agents such as alkyl chloroformates to give urethans. An additional benefit of the carbamate group is the option to convert it directly into an *N*-methyl group by reduction with e.g. lithium alanate. The phenethylamines required for this approach can be accessed from aromatic aldehydes by Henry reaction and subsequent reduction of resulting *β*-nitrostyrenes.

Further, an alternative to aldehydes should be investigated, since arylacetaldehydes, which would be required for the synthesis of benzyltetrahydroisoquinolines are often laborious to access and instable due to their tendency towards polymerization and autocondensation. As discussed before also masked aldehydes such as acetals[86-87], enamines[88-89], alkynes[90-91] and enol ethers[92] can be employed instead of aldehydes. Alkynes, nitrostyrenes - as precursor for the corresponding enamines - and enol ethers are investigated in preliminary model reactions in the following.

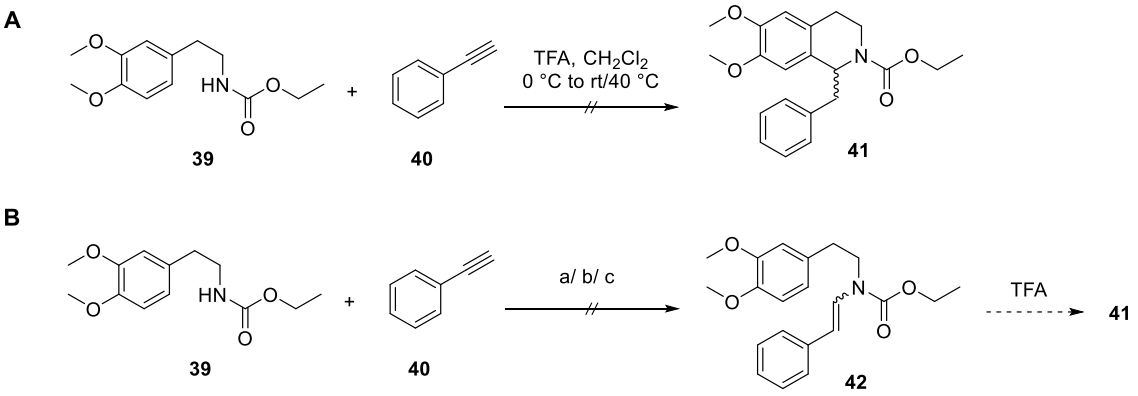
For this purpose known *N*-ethoxycarbonyl-3,4-dimethoxyphenethylamine (**39**) was chosen as *N*-acyl-arylethylamine building block, which was readily synthesized from commercially available 3,4-dimethoxyphenethylamine (**37**) and ethyl chloroformate (**38**) according to a literature method[104] (Scheme **9**).



Scheme 9. Synthesis of *N*-acyl-arylethylamine building block **39** serving as a model substrate in the following *N*-acyl Pictet-Spengler test reactions.

In a first attempt to investigate alkynes as building blocks for the Pictet-Spengler condensation, carbamate **39** was stirred with phenylacetylene (**40**) in the presence of trifluoroacetic acid

(TFA) in DCM following Vercauteren's approach[90] (Scheme **10**, **A**). Neither at ambient temperature nor under reflux conditions the desired cyclization product **41** could be generated, but a number of unidentified side products was detected instead (GC-MS and TLC control). Next, carbamate **39** was submitted to metal-catalyzed hydroamidation reaction to access the enamide **42** in the first place, which should then be cyclized under acidic conditions[105] to give **41**. To generate the enamide **42** two protocols of Gooßen *et al*.[106-107] were applied (Scheme **10**, **B**, methods a and b). In this approach a ruthenium catalyst (*in situ* generated from a ruthenium source and phosphine ligands) should promote the addition of carbamate **39** to phenylacetylene (**40**) in the presence of DMAP (and K_2CO_3 as base). Unfortunately no conversion to the desired enamide **42** could be observed (GC-MS control). Also the method of Herrero *et al*.[108] using $FeCl_3$ as catalyst in the presence of Cs_2CO_3 and pyridine was unsuccessful (Scheme **10**, **B**, method c).

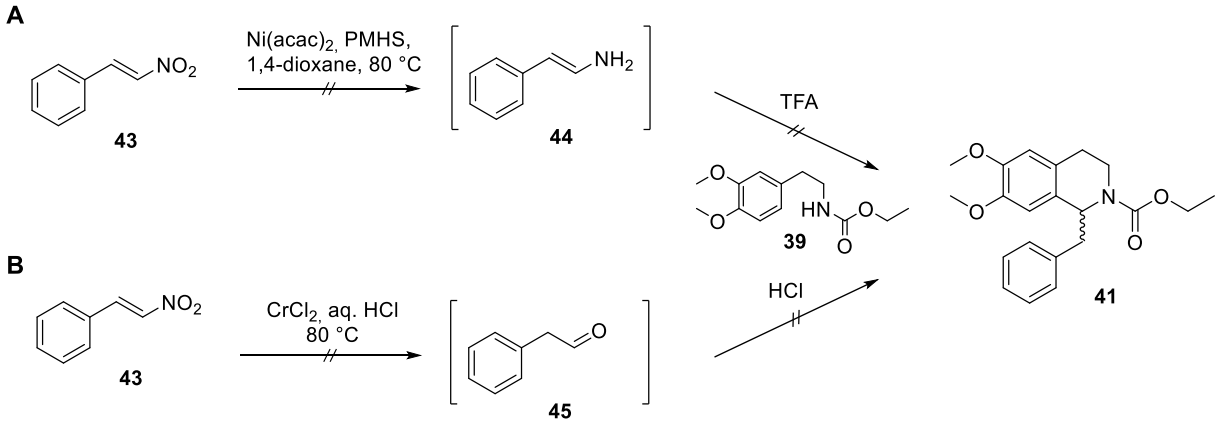


Scheme 10. Attempted synthesis of tetrahydroisoquinoline **41** *via* (**A**) Pictet-Spengler type reaction using alkyne **40** as aldehyde equivalent or (**B**) hydroamidation resulting in the enamide intermediate **42** susceptible for the subsequent TFA-catalyzed cyclization. Reaction conditions are listed below.

Table 1. Conditions for the hydroamidation reaction of carbamate **39** with phenylacetylene (**40**).

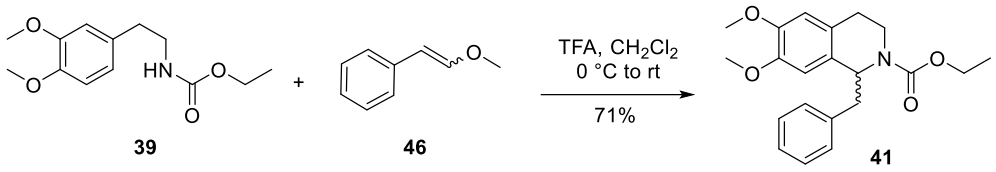
method	conditions	conversion
a[106]	carbamate **39** (1.0 eq.), alkyne **40** (2.0 eq.), 3 mol% $RuCl_3 \cdot 3\ H_2O$, 9 mol% P(*n*-Bu)$_3$, 9 mol% DMAP, 15 mol% K_2CO_3, 40 mol% H_2O, toluene, 100 °C	-
b[107]	carbamate **39** (1.0 eq.), alkyne **40** (1.3 eq.), 1 mol% ((*p*-cumene) $RuCl_2)_2$, 3 mol% P(*p*-Cl-C_6H_4)$_3$, 4 mol% DMAP, toluene, 60 °C	-
c[108]	carbamate **39** (1.0 eq.), alkyne **40** (1.0 eq.), 10 mol% $FeCl_3$, Cs_2CO_3 (1.0 eq.), 40 mol% pyridine, toluene, 150 °C (pressure tube)	-

In the next attempt the nitrostyrene **43** as precursor of enamine **44** was examined. *β*-Nitrostyrenes are easily available in one step from benzaldehydes and nitromethane *via* Henry reaction and therefore valuable building blocks. The commercially available *β*-nitrostyrene **43** was first submitted to a nickel-catalyzed reduction method using polymethylhydrosiloxane (PMHS) as reducing agent[109]. Hereby the nitro group should be selectively reduced to an amine resulting in the envisaged primary enamine **44** (Scheme **11**, **A**). Although this protocol was applied on the identical nitroalkene compound as described in the publication, there was no conversion observed (TLC control with the eluent system used by the authors for the purification of enamine **44**). Even at elevated temperatures (110 °C instead of 80 °C) or under microwave irradiation the reaction was unsuccessful. To rule out that the enamine is not detectable due to its susceptibility towards hydrolysis or other lability issues, the reaction was repeated in presence of carbamate **39** and an acid to instantly react the enamine **44** *via N*-acyl Pictet-Spengler condensation, but there was no reaction observed. Next, another reduction method was tested in which the intermediate is not an enamine but the corresponding phenylacetaldehyde (**45**) using $CrCl_2$ as reducing agent[110] (Scheme **11**, **B**). To avoid any possible stability issues of the generated phenylacetaldehyde, the reduction was conducted as one-pot approach in presence of carbamate **39**. As hydrochloric acid was required for the reduction protocol anyways, the acidic condition should promote the subsequent *N*-acyl Pictet-Spengler condensation once the aldehyde is generated *in situ*. Also this attempt did not lead to the desired product **41**.



Scheme 11. Attempted synthesis of tetrahydroisoquinoline **41** using *β*-nitrostyrene **43** after (**A**) reduction to enamine intermediate **44** or (**B**) conversion to phenylacetaldehyde **45**.

Following Comins' approach[111] enol ether **46** was now envisaged as aldehyde equivalent in the *N*-acyl Pictet-Spengler condensation with carbamate **39**, a method that was already applied successfully in our group before[112-113]. When reacting methoxystyrene **46** (commercially available) with carbamate **39** in the presence of TFA a full conversion within 2 h was observed and the desired cyclization product **41** was isolated in a yield of 71% (Scheme **12**), reproducing well the results of Dr. Alexandra Kamlah[112].



Scheme 12. Successful synthesis of tetrahydroisoquinoline **41** *via N*-acyl Pictet-Spengler reaction using enol ether **39** as aldehyde equivalent.

Once again the robustness of this protocol was demonstrated and the tetrahydroisoquinoline **41** was accessed in a good yield within a short reaction time. Moreover, *ώ*-alkoxystyrenes represent a benefical starting material as they should be readily available from benzaldehydes *via* Wittig olefination in a single operation. The *N*-acyl Pictet-Spengler reaction using *N*-ethoxycarbonyl-arylethylamine building blocks and *ώ*-alkoxystyrenes seems a fast and straightforward method for the construction of the tetrahydroisoquinoline moiety and therefore will be applied in the synthesis of the bisbenzylisoquinolines tetrandrine (**1**) and isotetrandrine (**2**) in the following.

2.2.2 SYNTHESIS OF TETRANDRINE (1)

This section is reproduced and partly adapted from ref. 1 with permission from The Royal Society of Chemistry.

In contrast to the published total syntheses of tetrandrine (**1**), the retrosynthetic approach aimed at utilizing *N*-acyl Pictet-Spengler cyclizations instead of Bischler-Napieralski protocols. This approach would provide tetrahydroisoquinolines directly, and further, by using *N*-alkoxycarbonyl residues in the *N*-acyl-arylethylamine building blocks, the required *N*-methyl groups should be available in only one additional step by lithium alanate reduction of the carbamate groups. This should lead to a significant reduction of the required number of steps. Alternatively, hydrolysis of the carbamate groups would provide secondary amino groups (N-2-*H*, N-2'-*H*), which in turn could subsequently be *N*-alkylated to give various tertiary amino groups. This should reduce the number of steps further compared to the original method, since *ώ*-alkoxystyrenes are available from the corresponding substituted benzaldehydes in one single step, whereas construction of arylacetic acids for Bischler-Napieralski reactions requires a number of steps. Further, the exploration of modern alternatives such as Buchwald-Hartwig coupling[114] or Chan-Evans-Lam reaction[71] for the construction of the diaryl ether moieties is aimed for.

Based on these considerations several alternative routes to tetrandrine (**1**) (and its isomers) were explored: In route 1 both 1-benzyltetrahydroisoquinoline moieties - meaning both stereocenters at C-1 and C-1' in consequence - were to be built up early in *inter*molecular *N*-

acyl Pictet-Spengler reactions, and the central step for the construction of the macrocycle should be an *intra*molecular diaryl ether synthesis at a late stage. In contrast, in route 2 a late *intra*molecular *N*-acyl Pictet-Spengler cyclization should provide the macrocycle under construction of the second stereocenter. For each route an additional variation was designed, considering that either the benzyltetrahydroisoquinoline moiety consisting of rings A-C or the one consisting of rings A'-C' can be constructed first. Besides the general feasibility of both approaches, the stereochemical outcome of all four conceivable variants was of high interest, as high diastereoselectivity of the whole protocol was desirable.

The sequence of the Pictet-Spengler- and C–O coupling steps of the four variants is depicted in Figure **8**. In detail, in the variants 1a and 1b the retrosynthetic approach for the synthesis of the macrocyclic skeleton consists of two alternating *N*-acyl Pictet-Spengler condensations and C–O couplings. Finally the macrocycle is generated in an *intra*molecular diaryl ether synthesis ("D-2") of a *seco*-bisbenzylisoquinoline intermediate, connecting rings C and C'. In route 2, both diaryl ethers are constructed early (operations "D-1" and "D-2") and the macrocycle is generated in an *intra*molecular *N*-acyl Pictet-Spengler condensation. In route 2a ring B' is constructed in this late operation ("P-S-2"), whereas in route 2b this final connection is performed for the construction of ring B ("P-S-1").

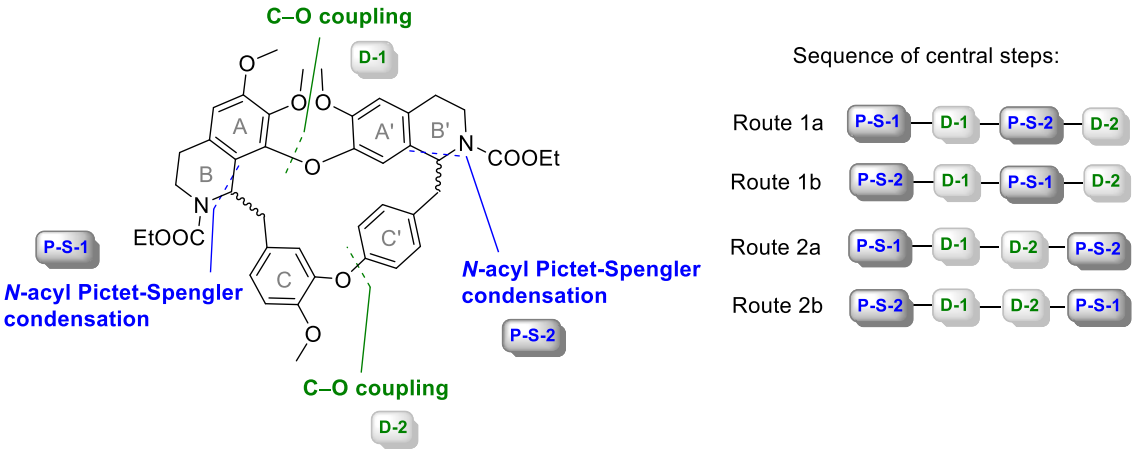


Figure 8. Retrosynthetic analysis of the envisaged routes to the precursor of racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**).

2.2.3 SYNTHESIS OF TETRANDRINE ANALOGUES

Based on the total synthesis of racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) the synthesis of full synthetic macrocyclic (iso)tetrandrine analogues is targeted. The flexible synthetic pathway should allow to implement variations on all of the four aromatic rings in tetrandrine (**1**), although this work will focus on structure variations exclusively on ring C. Hereby the general scope and limitation of this synthetic pathway should be investigated and

first structure variations should be made for initial structure-relationship studies. In pharmacological evaluations the substances will be screened for anticancer and multidrug reversing activities and assessed with respect to potential toxic effects.

As already discussed in the section “Toxicity of tetrandrine (**1**)” (chapter **1.2.5**) the methoxy group at C-12 in ring C (highlighted in red) is suspected to be responsible for tetrandrine’s (**1**) toxicity. A modification of ring C should be feasible by following route 1b or 2b. Aim is to either eliminate the critical methoxy group or to replace it by metabolically stable groups such as trifluoromethoxy or chlorine. Also a replacement of the benzene ring by different heterocycles (e.g. thiophene, furan and pyridine) or an alkyne chain is targeted. One intermediate of the tetrandrine synthesis that already covers the mutual scaffold (highlighted as bold bonds in Figure **9**) should be used as starting material. The bottom diaryl ether bridge connecting tail-to-tail should be constructed *via* suitable C–O bond forming reactions and the right tetradydroisoquinoline moiety *via* *N*-acyl Pictet-Spengler reaction using suitable (masked) aldehydes.

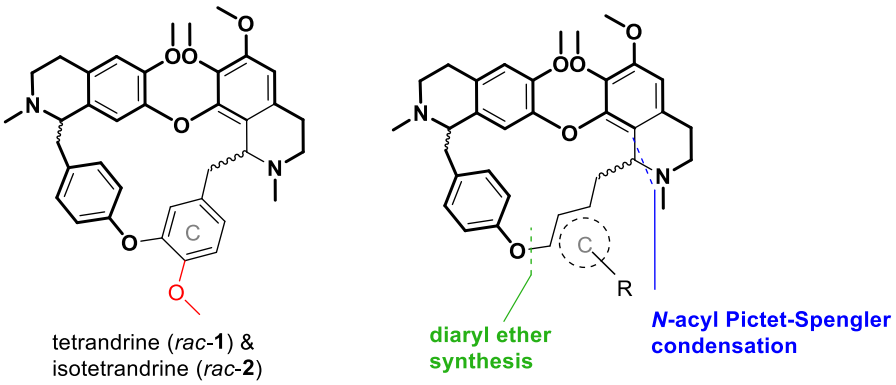


Figure 9. Structure of racemic tetrandrine (*rac*-**1**) & isotetrandrine (*rac*-**2**) and targeted macrocyclic compounds with variations on ring C. The bold bond indicates the identical scaffold present in both, the lead structure and the targeted analogues.

2.2.4 SYNTHESIS OF *SECO*-ANALOGUES

Besides the design and synthesis of macrocyclic tetrandrine analogues the synthesis of simplified *seco*-analogues is intended as well. Several biological activities of tetrandrine (**1**) are also documented for benzylisoquinolines e.g. anticancer[115-117] and calcium channel blocking[118] effects, which makes this class of alkaloids attractive since the synthetic access is easier and faster compared to bisbenzylisoquinoline alkaloids.

Within the scope of this thesis the synthesis of a small series of *seco*-analogues as exemplary truncated variants is planned. The analogues hereby should gradually converge the lead

structure tetrandrine (**1**). As a minimum all analogues comprise one benzylisoquinoline unit (rings A-C) as indicated by the bold lines in Figure **10**. Suitable intermediates of route 1a of the tetrandrine synthesis should serve as starting material. The benzenoid ring A' (highlighted in red) should be introduced *via* diaryl ether synthesis and ring B' should be constructed *via* *N*-acyl Pictet-Spengler reaction using different aldehydes (indicated by turquoise bonds). The ring C' should be mimicked by an *O*-benzyl residue at C-11.

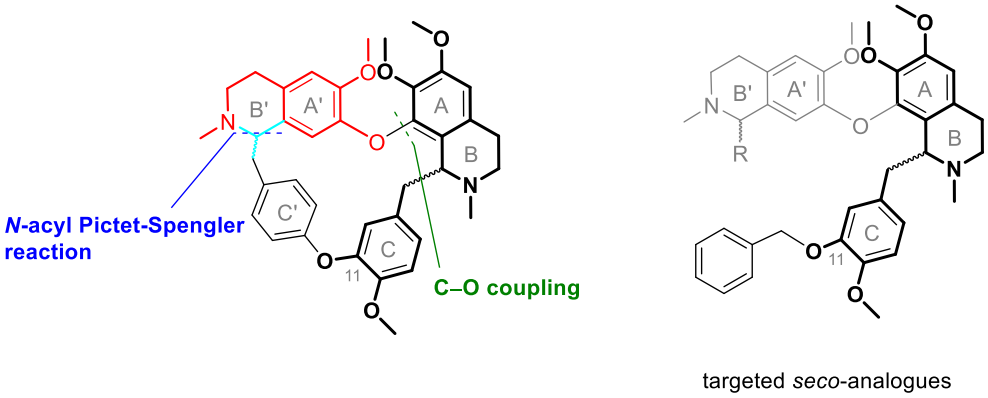


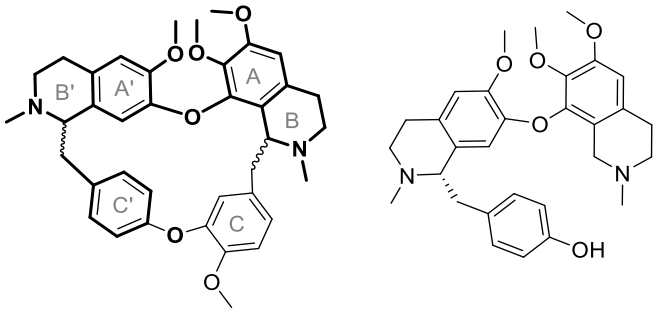
Figure 10. Synthetic approach for the targeted *seco*-analogues using suitable intermediates of the tetrandrine synthesis as starting material and C–O cross-coupling & *N*-acyl Pictet-Spengler reaction as key steps. The bold bonds indicate the mutual structural scaffold present in both, the lead structure and the targeted *seco*-analogues.

2.2.5 Related Alkaloids

Beside the bisbenzylisoquinolines tetrandrine (**1**) and isotetrandrine (**2**) the synthesis of further alkaloids containing a (tetrahydro)isoquinoline scaffold and a diaryl ether bridge is to be accomplished. Once a synthetic protocol for the construction of the central moieties is established as part of the synthesis of (iso)tetrandrine, the methods should be applied for the (racemic) total synthesis of the natural products muraricine (*rac*-**34**), berbanine (**35**) and berbidine (**36**) as well.

2.2.5.1 Muraricine

The isoquinoline-benzylisoquinoline alkaloid muraricine (**34**), recently isolated from *Berberis vulgaris* (Berberidaceae)[119], possesses the same scaffold like tetrandrine (**1**) as indicated by the bold lines in Figure **11**. The aromatic rings A and A' of the tetrahydroisoquinoline moiety display the same substitution patterns and an oxygen is present in *para*-position of the benzylic methylene group in both alkaloids. These similarities should allow to synthesize muraricine in its racemic form directly using an intermediate of the synthetic pathway of tetrandrine (**1**).



tetrandrine (*rac*-**1**) muraricine (**34**)

Figure 11. isoquinoline-benzylisoquinoline alkaloid muraricine (*rac*-**34**) and the structure of tetrandrine (**1**) with mutual structural elements highlighted as bold bonds.

2.2.5.2 BERBANINE AND BERBIDINE

For the synthesis of the dimeric isoquinoline-isoquinolone alkaloids berbanine (**35**) and berbidine (**36**), the 1-oxodihydroisoquinoline alkaloid thalifoline (**47**) should be used as starting material. The synthesis of thalifoline (**47**) was elaborated by Sandra Schmidt within the scope of her master's thesis in our group (for details see the published protocol[120]). The diaryl ether bridge should be constructed *via* a suitable C–O cross-coupling protocol of the phenolic compound **47** with either 2-bromo-3,4-dimethoxybenzaldehyde (**48**) or 8-bromo-6,7-dimethoxyisoquinoline (**49**, Figure **12**). The latter building block does not seem suitable for this type of cross-coupling reaction, as Knabe and coworkers[121] already failed to accomplish Ullmann couplings of this compound with a 7-hydroxyisoquinoline in their synthesis of the alkaloid phaeantharine. Since the more electron deficient and less sterically hindered 2-bromo-3,4-dimethoxybenzaldehyde (**48**) should undergo the conversion, this building block was chosen as coupling partner for the diaryl ether synthesis. The construction of the fully aromatic isoquinoline unit of alkaloid berbanine (**35**) should then be accomplished in a subsequent Pomeranz-Fritsch reaction. The *N*-methylation of berbanine (**35**) and the reduction of the resulting isoquinolinium salt should finally provide berbidine (**36**).

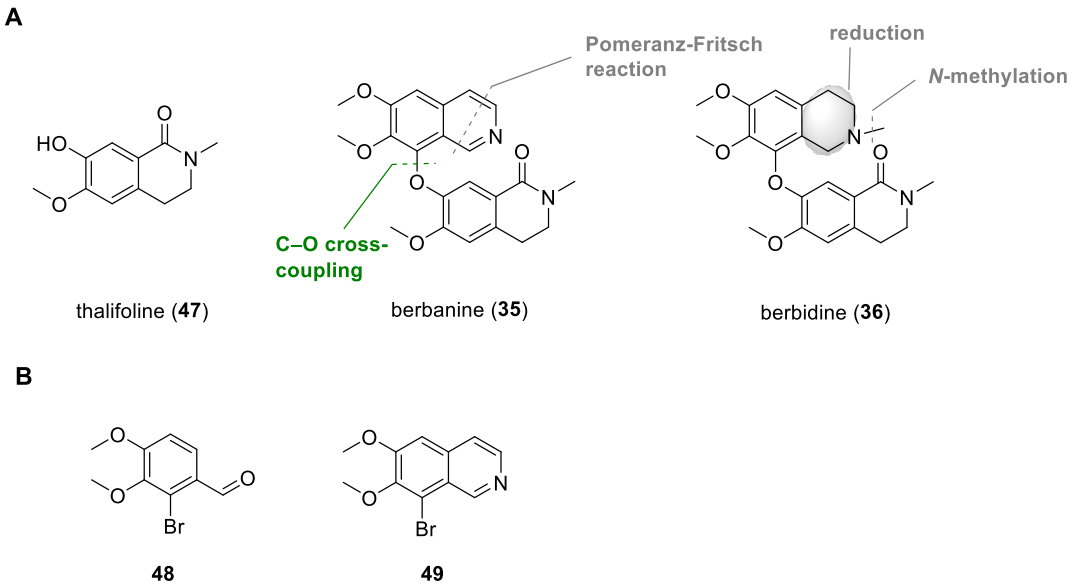


Figure 12. (**A**) 1-Oxodihydroisoquinoline alkaloid thalifoline (**47**) and the synthetic strategy for the dimeric isoquinoline-isoquinolone alkaloids berbanine (**35**) and berbidine (**36**). (**B**) 2-Bromo-3,4-dimethoxybenzaldehyde (**48**) and 8-bromo-6,7-dimethoxyisoquinoline (**49**) as potential building blocks for the envisaged C–O cross-coupling reaction.

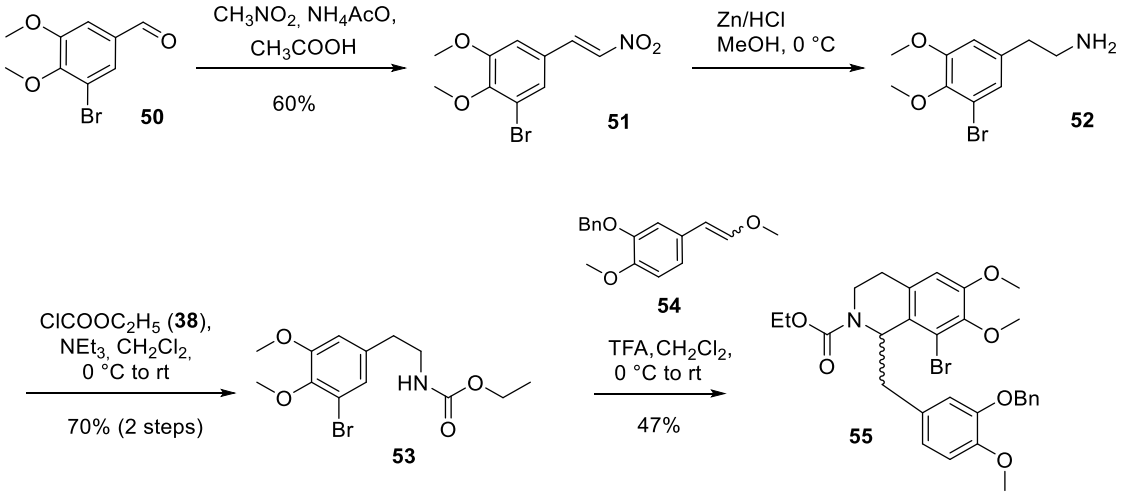
3 SYNTHESES

The synthesis of racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) was already pubslished in ref. 1. The synthesis and pharmacological evaluation of the analogues **RMS1**-**RMS10** was published in ref. 53., the data of racemic muraricine (*rac*-**34**) was published in ref. 122 and the synthesis of berbanine (**35**) and berbidine (**36**) in ref. 120.

3.1 SYNTHESIS OF TETRANDRINE (1)

As mentioned before several synthetic routes to racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) were elaborated. The two routes 1a and 1b start with the construction of either the one or the other benzylisoquinoline monomer, respectively, representing one half of the target molecule. The cyclization step in both routes 1a and 1b is an *intra*molecular diaryl ether synthesis. As an additional variation the routes 2a and 2b are to be developed, in which the macrocyclic system is constructed *via* an *intra*molecular *N*-acyl Pictet-Spengler. As the second asymmetric centre is to be generated simultaneously in this step, an asymmetric induction is to be expected generating preferably the one or the other diastereomer in consequence.

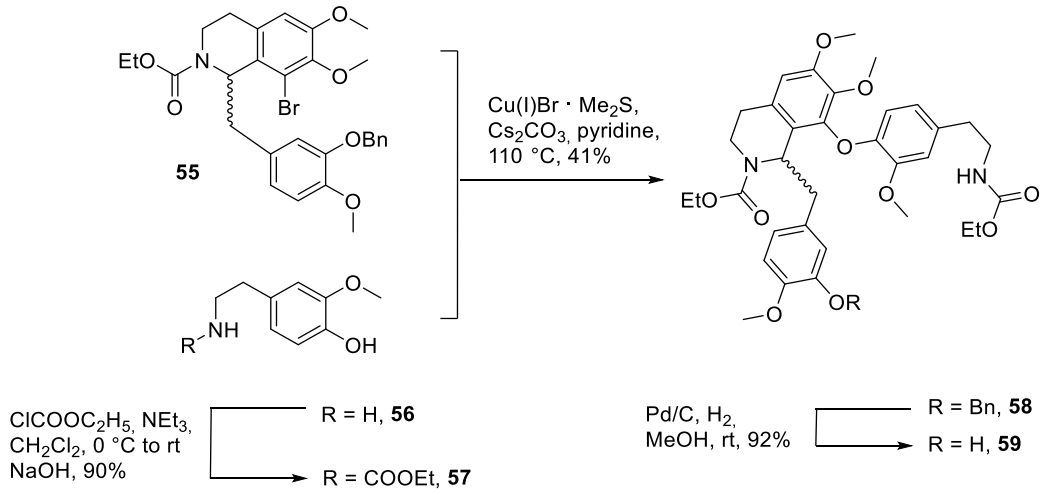
In route 1a the highly substituted 1-benzyltetrahydroisoquinoline **55**, which covers rings A-C of tetrandrine (**1**), was prepared from the commercially available aldehydes 5-bromoveratraldehyde (**50**) and *O*-benzylisovanilline. In a Henry reaction **50** was condensed with nitromethane[122] to give *ß*-nitrostyrene **51** in 60% yield. Reduction with zinc/HCl[122] gave the corresponding arylethylamine **52**, and subsequent reaction with ethyl chloroformate (**38**) led to carbamate **53** in 70% yield over both steps. Known enol ether **54**[123] was synthesized in a Wittig olefination of *O*-benzylisovanilline in 87% yield. The following *N*-acyl Pictet-Spengler condensation[111] with carbamate **53**, catalyzed by trifluoroacetic acid (TFA), gave racemic tetrahydroisoquinoline **55** in 47% yield (Scheme **13**). This moderate yield might be due to the sterically demanding bromine substituent. When using trifluoromethanesulfonic acid (TfOH) as a stronger acidic catalyst[84] instead, **55** was obtained in a comparable yield of 49%. Due to easier handling TFA was prefered in the following procedures. The *N*-acyl Pictet-Spengler condensation in this step delivers exclusively the desired regioisomer **55**. No by-product was identified in which cyclization took place at the *para* position of the bromine in intermediate **55**.



Scheme 13. Route 1a: Synthesis of the benzyltetrahydroisoquinoline **55**.

Next, the first C–O coupling was performed in order to obtain diaryl ether **58** (Scheme **14**). The required phenol **57** was prepared from commercially available 3-methoxytyramine (**56**; itself readily available from the aromatic aldehyde vanilline) and ethyl chloroformate (**38**). For the coupling of **55** with **57** several reaction conditions (Table **2**) were explored testing different ligand/catalyst systems. Palladium-catalyzed Buchwald-Hartwig cross-coupling reactions (Table **2**, entries 1-3) using different phosphine ligands[124] or Pd-PEPPSI™-IPr (**18**) as catalyst failed to furnish the desired diaryl ether **58**. Next a set of catalytic systems for Ullmann-type C–O couplings was explored employing different combinations of copper(I) halides, ligands and bases (entries 4-8). When using the combination of copper(I) iodide, *N,N*-dimethylglycine (**13**) and caesium carbonate in dioxane[68] traces of the desired product **58** (entry 4) were detected by LC-MS. Increasing catalyst and ligand to stoichiometric amounts (entry 5) did not improve the yield. Employing copper(I) bromide-dimethylsulfide complex with caesium carbonate in pyridine[125] without any additional ligand (entry 9) it was possible to isolate minor amounts (2%) of the desired diaryl ether **58**. A predominant side reaction was debromination of the aryl halide **55** at high reaction temperatures. Microwave conditions[126-127] instead of conventional heating could not improve the reaction in terms of yield and by-product formation (entry 10). To minimize debromination the temperature was decreased to 110 °C and the reaction time was prolonged. This modification resulted in a better yield (12%; entry 11). By increasing the amount of phenol **57** from 1.1 to 1.5 equivalents the yield was further improved to 27% (entry 12). The best result was obtained when performing the reaction at 110 °C with 2.0 equivalents of the phenol **57** furnishing diaryl ether **58** in 41% yield (entry 13). Considering the comparatively low reactivity of electron-rich and sterically hindered aryl halide **55**, the obtained yield is satisfying and comparable to the yield of 42% in Inubushi's approach[94] using related building blocks. An attempted Chan-Lam-Evans coupling[71] was discarded after the synthesis of the corresponding boronic acid from bromoarene **55** was unsuccessful. Diaryl ether **58** was then *O*-debenzylated by standard Pd-catalyzed hydrogenolysis giving phenol **59**

in 92% yield. The debenzylation had to be performed at this stage, since surprisingly the *O*-benzylated intermediate **58** was found to react very sluggishly in an attempted subsequent *N*-acyl Pictet-Spengler reaction with enol ether **60**.



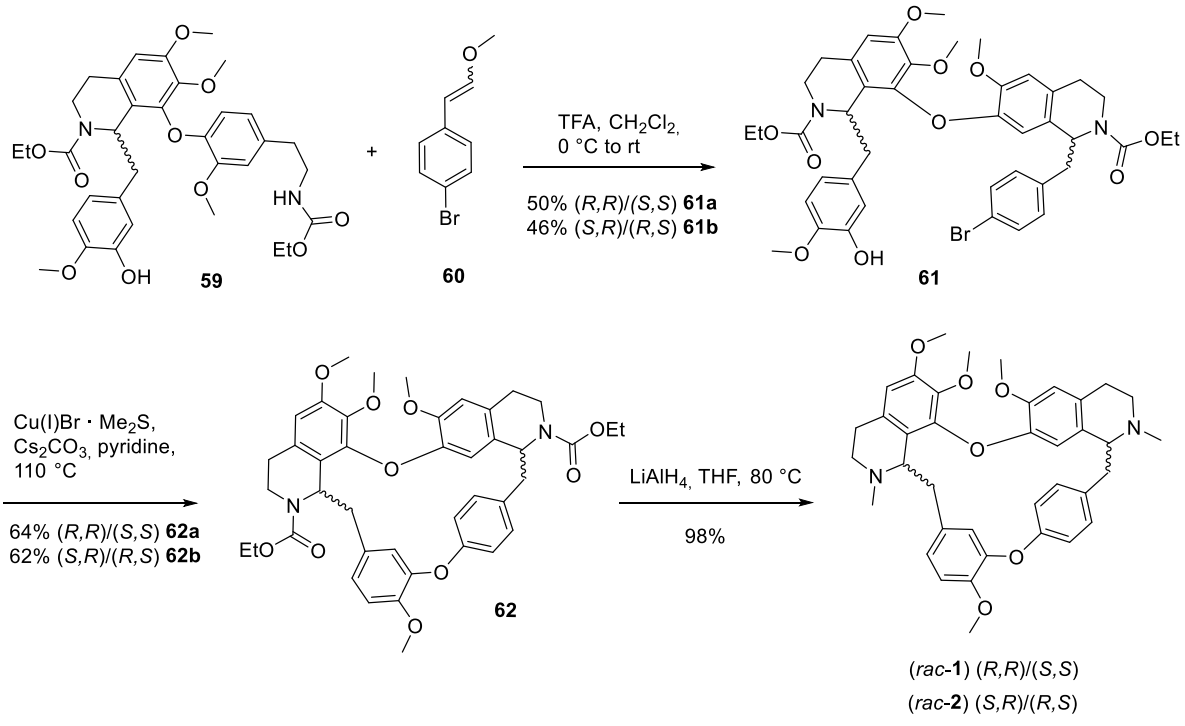
Scheme 14. Route 1a: First Ullmann coupling.

Table 2. Conditions for Ullmann-type C–O coupling of bromoarene **55** with penol **57**.

entry	conditions	eq. phenol 57	yield (%)
1	$Pd_2(dba)_3$ (1.5 mol %), tBuXPhos (**16**, 2.0 mol %), K_3PO_4 (2.0 eq.), toluene, 100 °C, 48 h[124]	1.2	-
2	$Pd(AcO)_2$ (5.0 mol %), Me_4tButylXphos (**17**, 7.0 mol %), K_3PO_4 (2.0 eq.), toluene, 100 °C, 48 h[124]	1.2	-
3	PEPPSI-IPr (**18**, 2.0 mol %), K_3PO_4 (2.0 eq.), toluene, 100 °C, 48 h	1.2	-
4	CuI (0.1 eq.), *N,N*-dimethylglycine (**13**, 0.3 eq.), Cs_2CO_3 (2.0 eq.), dioxane, 105 °C, 72 h, pressure tube[68]	1.5	traces
5	CuI (1.0 eq.), *N,N*-dimethylglycine (**13**, 3.0 eq.), Cs_2CO_3 (2.0 eq.), dioxane, 105 °C, 72 h, pressure tube[68]	1.5	traces
6	CuI (0.1 eq.), *N,N*-dimethylglycine (**13**, 0.3 eq.), Cs_2CO_3 (2.0 eq.), dioxane, 150 - 200 °C, 2.5 h, microwaves[126]	1.5	-
7	CuI (0.1 eq.), picolinic acid (**15**, 0.2 eq.), K_3PO_4 (2.0 eq.), DMSO, 90 °C, 72 h[70]	1.2	-
8	CuBr (1.0 eq.), 1,1'-azo*bis*(cyclohexanecarbonitrile) (**14**, 1.0 eq.), Cs_2CO_3 (2.0 eq.), DMF, 100 °C, 4 h, microwaves[69]	1.1	-
9	CuBr·Me_2S (1.0 eq.), Cs_2CO_3 (3.0 eq.), pyridine, 150 – 200 °C, 72 h, pressure tube[125]	1.1	2
10	CuBr·Me_2S (1.0 eq.), Cs_2CO_3 (3.0 eq.), pyridine, 220 °C, 3 h, microwaves	1.1	-

11	CuBr·Me_2S (1.0 eq.), Cs_2CO_3 (3.0 eq.), pyridine, 110 °C, 7 d	1.1	12
12	CuBr·Me_2S (1.0 eq.), Cs_2CO_3 (3.0 eq.), pyridine, 110 °C, 7 d	1.5	27
13	CuBr·Me_2S (1.0 eq.), Cs_2CO_3 (3.0 eq.), pyridine, 110 °C, 7 d	2.0	41

For the construction of the second tetrahydroisoquinoline moiety the method of choice was again a TFA-mediated *N*-acyl Pictet-Spengler condensation, connecting intermediate **59** with known enol ether **60**[128] to give *seco*-bisbenzylisoquinoline **61** in an excellent yield of 96% (Scheme **15**) and again with desired regioselectivity. As expected both racemic diastereomers in a ratio of 1:1 (determined by HPLC) were obtained. No stereocontrol was observed, since the newly formed stereocenter is far away from the stereocenter in the starting material. But fortunately, the obtained diastereomers of **61** were easily separated by flash column chromatography on a preparative scale. The isolated yields of the racemic diastereomers were 50% of the (*R*,*R*)/(*S*,*S*) isomers (**61a**) and 46% of the (*R*,*S*)/(*S*,*R*) isomers (**61b**). The relative configurations of these products were determined retrospectively after conversion into racemic tetrandrine (*rac*-**1**) and racemic isotetrandrine (*rac*-**2**), respectively.



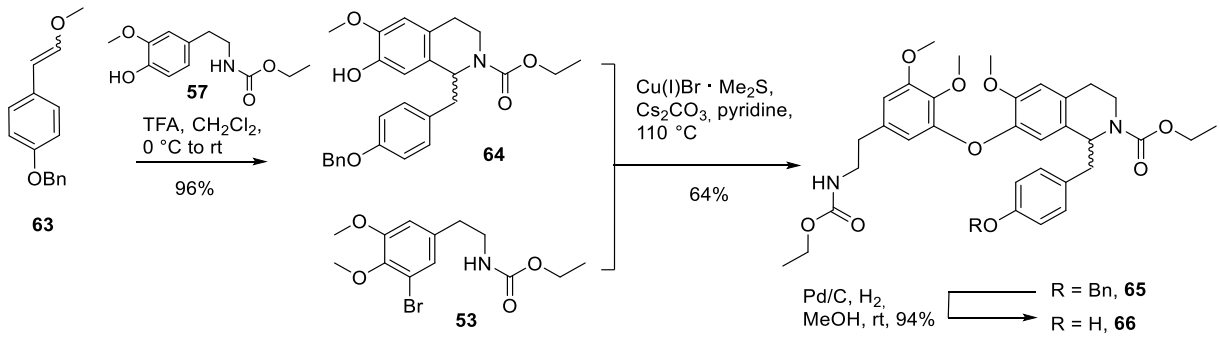
Scheme 15. Route 1a: Synthesis of racemic tetrandrine (*rac*-**1**) and racemic isotetrandrine (*rac*-**2**) *via seco*-bisbenzylisoquinoline **61**.

For the following *intra*molecular C–O coupling to generate the macrocycle **62** once again a screening for reaction conditions was conducted. $Pd_2(dba)_3$ in combination with phosphine ligand Me_4tButylXphos (**17**)[124], copper(I) iodide combined with ligand *N,N*-dimethylglycine

(**13**)[68] and copper(I) bromide-dimethylsulfide complex[125] were tested as catalytic systems on a mixture of diastereomers **61** (compare entries 2, 4 and 11 in Table **2**). All of these reactions were carried out under high dilution conditions (0.02 M) in order to suppress *inter*molecular coupling reactions. Again copper(I) bromide-dimethylsulfide complex catalyzed the diaryl ether synthesis well, furnishing the desired macrocycle **62** in 62-64% yield (Scheme **15**), whereas the other catalytic systems were not successful. Surprisingly the separation of diastereomers of **62** *via* flash column chromatography could not be achieved. Thus, for generation of pure racemic alkaloids the cyclization had to be conducted with the previously isolated racemic diastereomers of the *seco*-intermediate **61**. Both isomers were cyclized in almost identical yields of 62 and 64%.

To complete the total synthesis of the alkaloids, carbamates **62** were reduced using $LiAlH_4$ in THF to give racemic tetrandrine (*rac*-**1**) and racemic isotetrandrine (*rac*-**2**), both in almost quantitative yield (98%) (Scheme **15**). The analytical data of racemic tetrandrine (*rac*-**1**) was identical with those of an authentic natural sample of tetrandrine (**1**), kindly donated by Prof. Peter Pachaly.

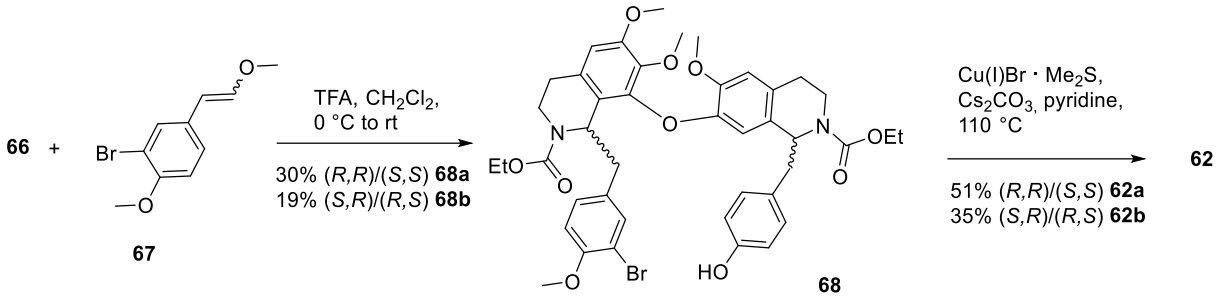
As a variation of this approach route 1b was elaborated, which starts with the synthesis of the benzyltetrahydroisoquinoline unit consisting of rings A'-C'. Following the established protocol of TFA-catalyzed *N*-acyl Pictet-Spengler reaction, carbamate **57** was condensed with known enol ether **63**[129] to give racemic 1-benzyltetrahydroisoquinoline **64** in 96% yield (Scheme **16**). Enol ether **63** was synthesized by Wittig olefination of commercially available 4-benzyloxybenzaldehyde in 97% yield. For the Ullmann synthesis of diaryl ether **65** from phenolic intermediate **64** and aryl bromide **53** (see Scheme **13**) once again the established catalytic system was employed (Scheme **16**).



Scheme 16. Route 1b: Synthesis of diaryl ether **65**.

This critical key step could significantly be enhanced in this approach compared to route 1a (Scheme **14**). The diaryl ether was now obtained in a yield of 64% (vs. 41%) in a shorter reaction time (3 days vs. 7 days). Also in terms of efficiency this step was improved, since only 1.0 equivalents of phenol instead of 2.0 equivalents was brought to reaction with 1.2

equivalents of aryl bromide **53**. The improved yield can be explained by the fact that aryl bromide **53** is less sterically hindered than the aryl halide **55** in route 1a. Diaryl ether **65** was further debenzylated by hydrogenolysis in methanol to give phenol **66** in 94% (Scheme **16**).



Scheme 17. Route 1b: Synthesis of *seco*-bisbenzylisoquinoline **68** and cyclization.

Next *seco*-bisbenzylisoquinoline **68** was obtained in an *N*-acyl Pictet-Spengler reaction of **66** with enol ether **67**[130], which was prepared in 80% yield by Wittig olefination of the corresponding aromatic aldehyde. Surprisingly the product of this Pictet-Spengler reaction following the standard protocol was not an equimolar racemic mixture of diastereomers (compared to route 1a), but the (*R*,*R*)/(*S*,*S*) isomers (**68a**) were formed preferably (ratio 62:38, determined by HPLC) in an isolated yield of 30% (Table **3**, entry 1), whereas the (*S*,*R*)/(*R*,*S*) isomers (**68b**) were obtained in 19% yield. As in route 1a, the diastereomers were easily separable using flash column chromatography. Further, a by-product was isolated in 24% yield, which was identified as another Pictet-Spengler product with the same mass as the desired product. Since the fraction of the by-product was an inseparable mixture of diastereomers, exact identification was not possible, but most likely it is a regioisomer of *seco*-bisbenzylisoquinoline **68**, resulting from cyclization to the other free *ortho* position of precursor **66**. In order to decrease the amount of this by-product and to improve the diastereomeric ratio, the *N*-acyl Pictet-Spengler reaction was performed under different conditions (Table **3**). Conducting the reaction at lower temperature (entry 2) had only minor influence in terms of diastereomeric ratio and the formation of the by-product. Using trifluoromethanesulfonic acid (TfOH) instead of TFA (entry 3) increased the formation of (*S,R*)/(*R,S*) isomers, leading to a more balanced ratio of 47:53, but did not decrease by-product formation. Following Kayhan's approach[131], the reaction was conducted in the more polar solvent trifluoroethanol (entry 4), ending up with an improved regioselectivity of 80:20. A diastereomeric ratio of 54:46 was obtained hereby for the desired regioisomer **68**. Even though the regioselectivity was best in this entry, due to a slow and incomplete conversion it was decided to follow the established protocol (entry 1) for the synthesis of *seco*-bisbenzylisoquinoline **68** (Scheme **17**).

Table 3. Route 1b: Conditions for the synthesis of *seco*-bisbenzylisoquinoline **68**.

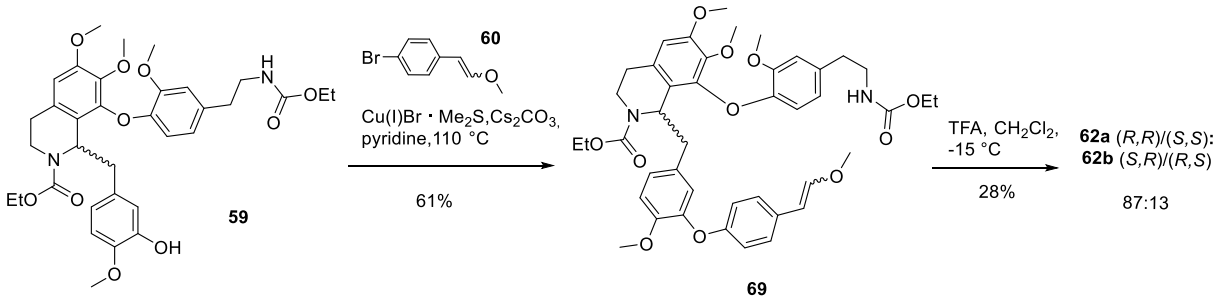
entry	solvent	acid	temperature (°C)	ratio (*S,S*)/(*R,R*):(*S,R*)/(*R,S*)	product/by-product
1	DCM	TFA	rt	62:38	68:32
2	DCM	TFA	-15	66:34	66:34
3	DCM	TfOH	rt	47:53	69:31
4	TFE	TFA	rt	54:46	80:20

In the following step the macrocycle **62** was generated *via intra*molecular C–O coupling of **68** (with previously separated racemic diastereomers) using the protocol as described above, yielding 51% of macrocyclic (*R*,*R*)/(*S*,*S*) isomers (**62a**) and 35% of (*S*,*R*)/(*R*,*S*) isomers (**62b**, Scheme **17**). Both of these products can be reduced to racemic tetrandrine (*rac*-**1**) and racemic isotetrandrine (*rac*-**2**), respectively, in almost quantitative yields, as shown for route 1a (Scheme **15**).

As expected and discussed above, both routes 1a and 1b gave mixtures of diastereomers. Fortunately, chromatographic separation of late intermediates was achieved in both routes, so both racemic tetrandrine (*rac*-**1**) and racemic isotetrandrine (*rac*-**2**) are available in pure form with these approaches. Nevertheless, it was intended to expand this approach to a protocol with preference for the one or other of the diastereomers. Altering the sequence of reaction steps, particularly utilizing an *intra*molecular *N*-acyl Pictet-Spengler reaction for ring closure and construction of the second stereocenter, should presumably lead to an asymmetric induction as a result of the influence of the stereochemistry of the already present asymmetric center and pre-organization of the chiral starting material. This aim was achieved in routes 2a and 2b, as elaborated in detail in the following.

In route 2a, employing the established diaryl ether synthesis protocol, phenolic intermediate **59** from route 1a was coupled with 4-bromophenyl enol ether (**60**) to obtain **69** in 61% yield (Scheme **18**). Next the reaction conditions for the *intra*molecular *N*-acyl Pictet-Spengler condensation were examined. The reaction was carried out at different temperatures (Table **4**), expecting that the stereochemical outcome might be controlled by the reaction temperature to a certain extent. No conversion was observed below -20 °C using TFA as catalyst (entry 1). At -20 °C, catalyzed by TFA, macrocycle **62** was formed in 13% yield under predominant formation of the (*R,R*)/(*S,S*) isomers **62a** (diastereomeric ratio d.r. 84:16; entry 2), hence favouring the relative stereoconfiguration of tetrandrine (**1**) (*S,S*) and its enantiomer phaeanthine (*R,R*). The best result was obtained at -15 °C (entry 3) in terms of diastereomeric ratio (87:13) and yield (28%). When performing the reaction at ambient temperature a comparable yield (25%) was obtained and a d.r. of 82:18 (entry 4). With the stronger acid

trifluoromethanesulfonic acid (TfOH) macrocycle **62** was generated even at -78 °C, but in a very poor yield of 9% in a 78:22 ratio (entry 5). With toluenesulfonic acid (*p*-TsOH) no noteworthy reaction was observed below 40 °C, and at elevated temperature only inferior d.r. and poor yield was obtained (entry 6). Eventhough the cyclization step of route 2b suffers from low yield, the asymmetric induction in this step is remarkable and motivating to do further investigations.



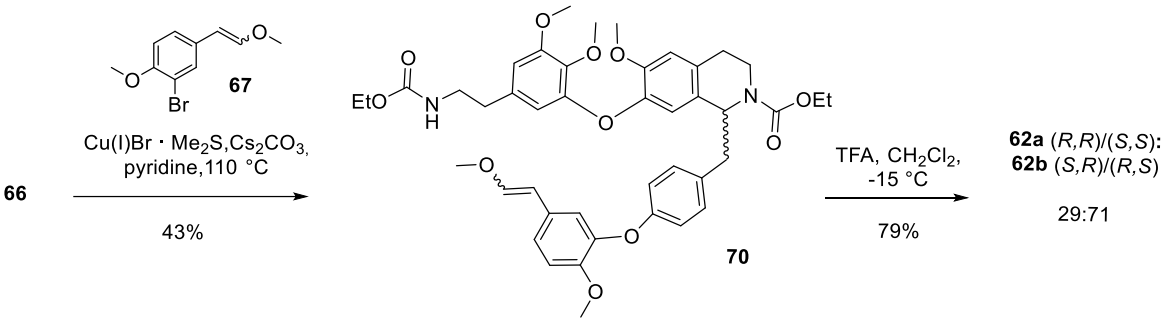
Scheme 18. Route 2a: Cyclization *via intra*molecular Pictet-Spengler condensation.

Table 4. Conditions for cyclization *via N*-acyl Pictet-Spengler condensation.

entry	**temperature** (°C)	**acid**	**ratio** (*R,R*)/(*S,S*):(*S,R*)/(*R,S*)	**yield** (%)
1	-78 to -25	TFA	-	-
2	-20	TFA	84:16	13
3	-15	TFA	87:13	28
4	20	TFA	82:18	25
5	-78	TfOH	78:22	9
6	40	*p*-TsOH	62:38	> 5

Route 2a involved late stage construction of the tetrahydroisoquinoline moiety (rings A' + B') forming the stereocenter at C-1', but the same concept can also be applied to C-1 in ring B. So, in route 2b, the same building blocks were used as in route 1b, but the Ullmann coupling was performed first, followed by an *intra*molecular Pictet-Spengler reaction. Diaryl ether **70** was obtained from phenolic intermediate **66** and brominated enol ether **67** employing the established diaryl ether synthesis protocol in a yield of 43% (Scheme **19**). Important for this step is the use of freshly synthesized enol ether **67**, since it tends to decompose quickly resulting in minor yields. In attempts to improve this yield once again Pd-catalysis (compare entry 2 in Table 1) was examined, but only traces of the desired product **70** were obtained. In the subsequent *intra*molecular Pictet-Spengler reaction, catalyzed by TFA at -15 °C, macrocycle **62** was obtained in 79% yield (Scheme **19**), but in strong contrast to route 2a, here

the isotetrandrine-type (*S,R*)/(*R,S*) isomers **62b** were formed predominantly in a ratio of 71:29 (determined by HPLC). In contrast to route 1b, where regioisomeric products were obtained in *inter*molecular Pictet-Spengler reactions, exclusively the desired cyclization products were detected in this *intra*molecular reaction. Whereas route 2a does not provide an advantage over route 1a in terms of yield, the access of isotetrandrine-type isomers in route 2b could be improved compared to route 2a.



Scheme 19. Route 2b: Alternative cyclization *via intra*molecular *N*-acyl Pictet-Spengler condensation.

Final step of both routes 2a and 2b was, as in routes 1a and 1b, the reduction of both ethyl carbamate moieties in **62** using $LiAlH_4$ in THF to give *N*-methyl groups, ending up in with mixtures of racemic tetrandrine (*rac*-**1**) and racemic isotetrandrine (*rac*-**2**) (see Scheme **15**). Separation of these diastereomers is possible using preparative TLC[132] or preparative HPLC, so pure racemic alkaloids can also be obtained *via* routes 2a and 2b.

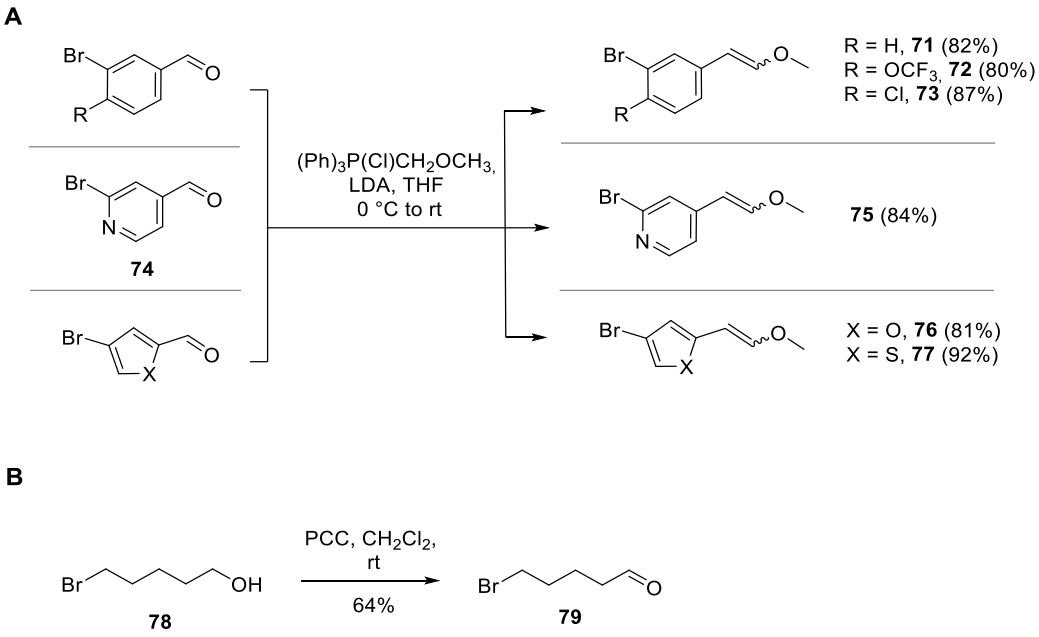
In Inubushi's synthetic approach[96], which included an *intra*molecular Bischler-Napieralski reaction, some stereocontrol was also observed favouring the formation of tetrandrine-type (*R*,*R*)/(*S*,*S*) isomers. In this case the second stereocenter was not built up in the course of the cyclization reaction, but in the following reduction of the formed 3,4-dihydroisoquinoline moiety to the corresponding tetrahydroisoquinoline. The best d.r. obtained there was 4:1 (determined by NMR).

3.2 SYNTHESIS OF TETRANDRINE ANALOGUES

Once the synthetic pathway for racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) was established, fully synthetic analogues of tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) were designed and synthesized. As mentioned above, structure variations hereby focus on ring C, which bears the hypothesized metabolically labile 12-methoxy group. In the targeted compounds the critical methoxy group is to be eliminated or replaced by metabolically stable functional groups such as trifluoromethoxy or chlorine substituents. These variations should already be sufficient for investigating the role of the methoxy group at C-12 for the toxicity of tetrandrine (**1**). If the hypothesized pathway is indeed the underlying mechanism for tetrandrine-induced toxicity, a significant reduction of toxic effects should be achieved herewith. To further explore structure-activity relationships the synthesis of structure variations containing different aromatic heterocycles or a simple alkyl chain instead of ring C is aimed for.

For the synthesis of the targeted compounds a synthetic route is to be selected, in which ring C is inserted in a late stage. This is possible in route 1b, in which ring C is introduced by an *N*-acyl Pictet-Spengler reaction and a subsequent Ullmann coupling. Also route 2b is basically feasible, in which the sequence of these two steps is reversed. As shown in the synthesis of (iso)tetrandrine, preferably macrocyclic intermediates with the stereoconfiguration of isotetrandrine (**2**) *via* asymmetric induction are formed in this route, whereas in route 1b no or just a slight preference for tetrandrine-like intermediates was observed. In this project the synthesis of both, tetrandrine- as well as isotetrandrine-type analogues is aimed for, as the influence of relative stereochemistry on biological targets is of interest. In addition, the feasibility of route 2b depends on the stability of employed enol ethers, which need to sustain the harsh conditions required for the Ullmann coupling reaction. Based on these considerations route 1b was chosen for the synthesis of (iso)tetrandrine analogues, especially as the required enol ethers turned out to be quickly decomposing, as discussed later.

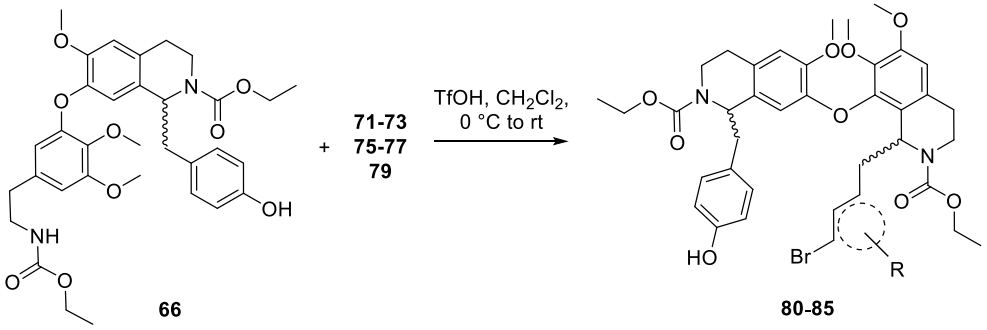
As starting material the intermediate **66** of the (iso)tetrandrine synthesis was utilized, which was readily synthesized in a larger scale. Next step was the synthesis of the required enol ethers for the construction of ring C. The enol ethers **71**-**73** and **75**-**77** were prepared *via* Wittig olefination of the corresponding commercially available aromatic aldehydes (Scheme **20**, **A**) in high yields (80-92%) following the established standard protocol. For the planned alkyl analogue commercially available 5-bromo-1-pentanol (**78**) was oxidized using pyridinium chlorochromate (PCC)[133] to the corresponding aldehyde (Scheme **20**, **B**).



Scheme 20. (**A**) Synthesis of the enol ethers **71**-**73** and **75**-**77** *via* Wittig olefination. (**B**) Synthesis of aldehyde **79** *via* oxidation of 5-bromo-1-pentanal (**78**).

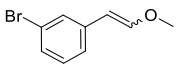
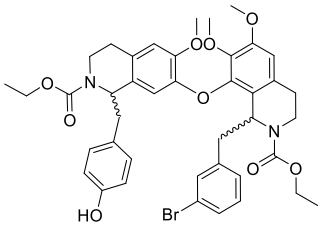
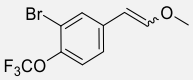
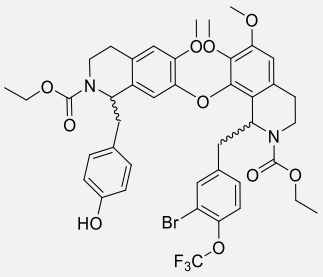
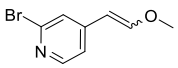
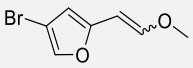
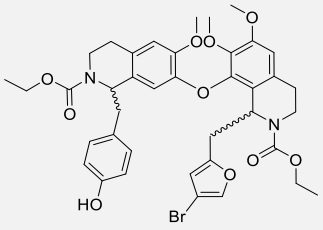
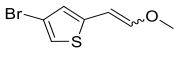
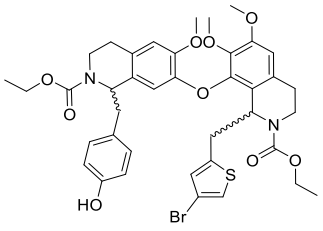
As already mentioned these enol ethers were not as stable as the enol ethers **60** and **67** previously used for the (iso)tetrandrine synthesis. Eventhough the NMR spectra of the compounds recorded right after isolation displayed no or only minor peaks of impurities, in the HPLC chromatogram several peaks as a result of decomposition were visible after some time and also the visual appearance changed quickly.

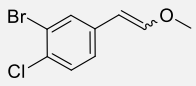
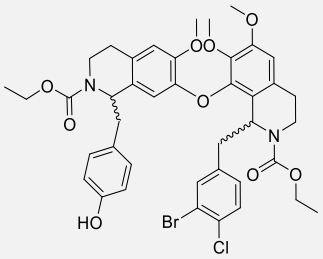
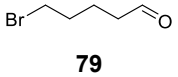
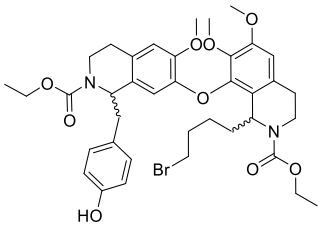
With the building blocks **71**-**73**, **75**-**77** and **79** in hand an *inter*molecular *N*-acyl Pictet-Spengler reaction was then conducted with the carbamate intermediate **66** of the (iso)tetrandrine synthesis (Scheme **21**). Trifluoromethanesulfonic acid (TfOH) was used as catalyst, since as observed previously in the synthesis of (iso)tetrandrine, catalysis utilizing TfOH resulted in an almost equimolar diasteromeric ratio of tetrandrine/isotetrandrine-like intermediates (d.r. of 47:53 (*S,S*)/(*R,R*):(*S,R*)/(*R,S*)). Under TFA-catalysis preferably tetrandrine-like precursors were formed in a d.r. of 62:38 (see Table **3**) in route 1b of the (iso)tetrandrine synthesis. As both tetrandrine- as well as isotetrandrine-like analogues are desired, TfOH was preferentially used here.



Scheme 21. Synthesis of *seco*-bisbenzylisoquinolines **80**-**85** *via* *N*-acyl Pictet-Spengler reaction.

Table 5. *Seco*-bisbenzylisoquinolines **80**-**85**. *isolated yield (sum of diastereomers). **the stereoconfiguration of the bromobutyl intermediates **85** could not be determined.

entry	enol ether/ aldehyde	product	yield* (%)	diastereomeric ratio (*S*,*S*)/(*R*,*R*):(*S*,*R*)/(*R*,*S*)
1	 **71**	 **80**	64	54:46
2	 **72**	 **81**	63	60:40
3	 **75**	-	-	-
4	 **76**	 **82**	24	50:50
5	 **77**	 **83**	68	51:49

6	 **73**	 **84**	53	49:51
7	 **79**	 **85**	59	61:39**

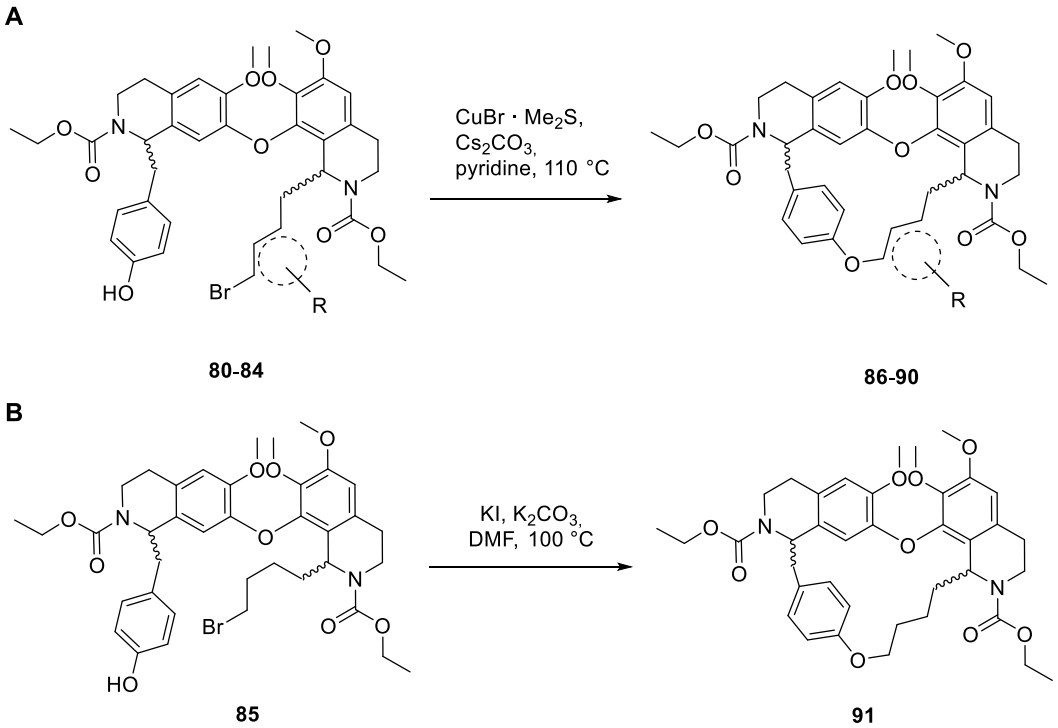
The *inter*molecular *N*-acyl Pictet-Spengler condensation proceeded well in yields ranging from 48-64% (sum of diasteromers), except for the furan and pyridine variation (entry 3 and 4, Table **5**). TLC control of the *N*-acyl Pictet-Spengler reaction of carbamate **66** with furanyl enol ether **76** indicated a notable formation of side products and the yield for both diastereomers in sum amounted only 24% (entry 4, Table **5**). The diminished yield can be explained by the sensitivity of the furan moiety towards acids[134]. The pyridine variation **75** did not react at all under the standard reaction conditions using TfOH, although an additional equivalent of acid was used (1.1 equivalents in total) on top of the usual catalytic amount (0.1 equivalents), as one equivalent is probably consumed by the protonation of the basic pyridine (entry 3, Table **5**). Neither elevated temperatures (40 °C) nor the use of other acids such as TFA or sulfuric acid in excess amounts could bring the enol ether **75** to reaction. The latter attempt was conducted in acetic acid employing concentrated sulfuric acid, following Ponnala's protocol[135], in which 3-bromo-4-pyridinecarboxaldehyde was reacted likewise with an acylated phenethylamine in an *N*-acyl Pictet-Spengler in good yield. Since this approach didn't obviously work out in this case, the pyridine variation was discarded.

As already described for route 1b in the synthesis of (iso)tetrandrine, the *inter*molecular *N*-acyl Pictet-Spengler condensation proceeds racemic and not in a regioselective manner. In consequence, a mixture of diastereomers and regioisomers is generated in this step. Luckily, the *seco*-intermediates **80**-**85** that respresent the desired regioisomers, were always preferably formed and it was possible to separate them from the side products by flash column chromatography. The undesired regioisomers, which were formed due to two possible directions in the cyclization step as aforementioned, were isolated in minor amounts ranging from 13-25%. An unambiguous identification of the correct isomers was conducted by NMR analysis (HMBC experiments). The diastereomeric mixture of the intermediates **80**-**85** was

successfully separated by FCC as well, so that the open-chain diastereomers could be proceeded separately in the next step.

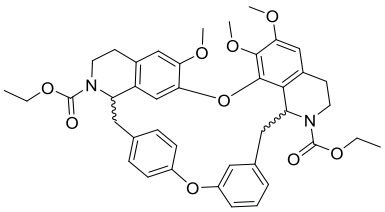
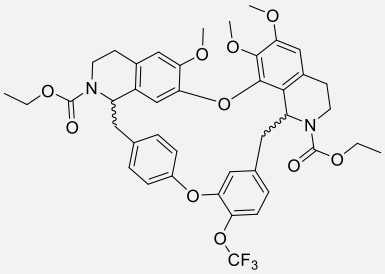
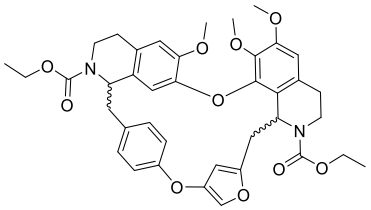
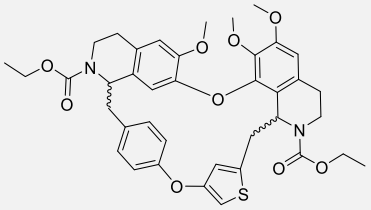
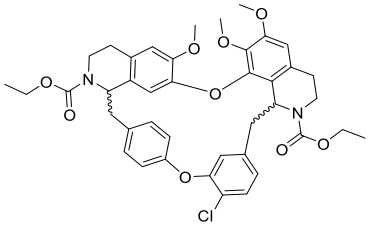
The isolated diastereomers of *seco*-intermediates **80**-**85** were now reacted in an *intra*molecular Ullmann coupling (Scheme **22**, **A**) following the established protocol to construct the diaryl ether bridges (connecting rings C and C') furnishing the macrocyclic bisbenzylisoquinolines **86**-**90** in yields from 17-77% as summarized in Table **6**. The *ω*-bromobutyl intermediate **85** was processed *via* S_N2 reaction in DMF employing K_3PO_4 as base in the presence of catalytic amounts of potassium iodide (Scheme **22**, **B**) to give macrocyclic intermediate **91** in yields of 29 and 60% respectively (entry 6, Table **6**). Again the variation **82** containing a furanyl residue led to unsatisfactory results, as only traces of the macrocyclic intermediate **88** could be detected by LC-MS (entry 3, Table **6**). Since both steps, the synthesis of the *seco*-intermediate **82** and its conversion to the macrocyclic compound **88** proceeded very poorly, the furanyl variation was discarded.

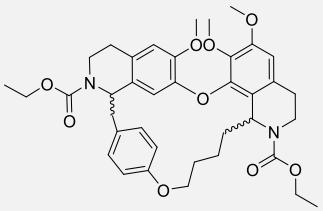
In general it was observed that the rate of cyclization strongly depended on the relative stereochemistry of the *seco*-intermediates. In most cases the *S*,*S*/*R*,*R* intermediates gave approximately twice as high yields than the *S*,*R*/*R*,*S* intermediates.



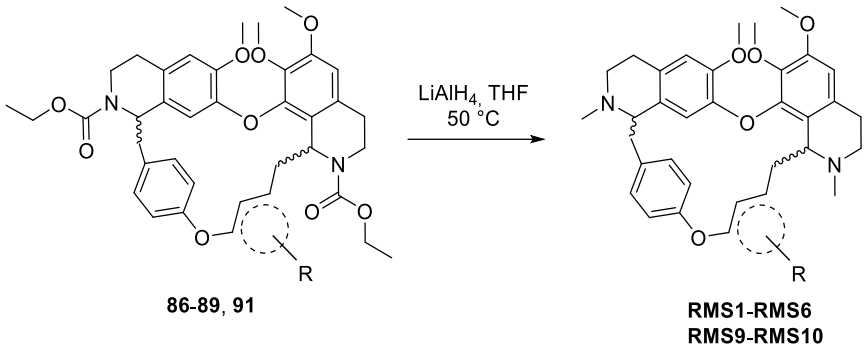
Scheme 22. Reaction conditions for the synthesis of macrocyclic bisbenzylisoquinolines **86**-**91**. (**A**) *Intra*molecular Ullman-type cross-coupling of *seco*-intermediates **86**-**90**. (**B**) S_N2 reaction of *ω*-bromobutyl intermediate **91**.

Table 6. Yields of the synthesis of macrocyclic bisbenzylisoquinoline intermediates **86**-**90** *via* Ullmann coupling or S_N2 reaction, respectively. *the stereoconfiguration of the butylidene intermediate **91** could not be determined.

entry	*seco*-intermediate	product	**yield** (%) (*S,R*)/(*R,S*)	(*S,S*)/(*R,R*)
1	**80**	 **86**	40	77
2	**81**	 **87**	28	64
3	**82**	 **88**	traces	
4	**83**	 **89**	17	57
5	**84**	 **90**	25	49

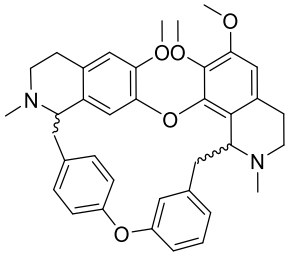
6	**85**	 **91**	29*	60*

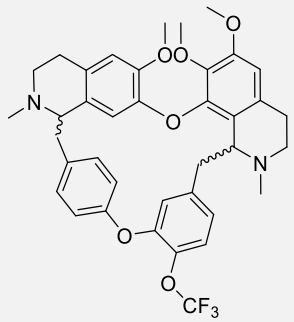
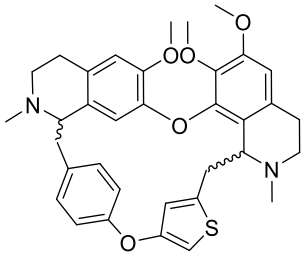
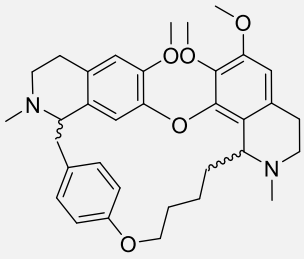
To obtain the desired *N*-methylated compounds **RMS1**-**RMS6** and **RMS9**-**RMS10** both carbamate groups were simultaneously reduced using lithium alanate in a final step (Scheme **23**). Following the standard protocol established in the synthesis of (iso)tetrandrine the reaction proceeded straightforward in good to almost quantitative yields ranging from 62-94% (Table **7**).



Scheme 23. Reaction conditions for the reduction of carbamate groups in the bisbenzylisoquinoline precursors **86**-**89** and **91** to give the final compounds **RMS1**-**RMS6** and **RMS9**-**RMS10**.

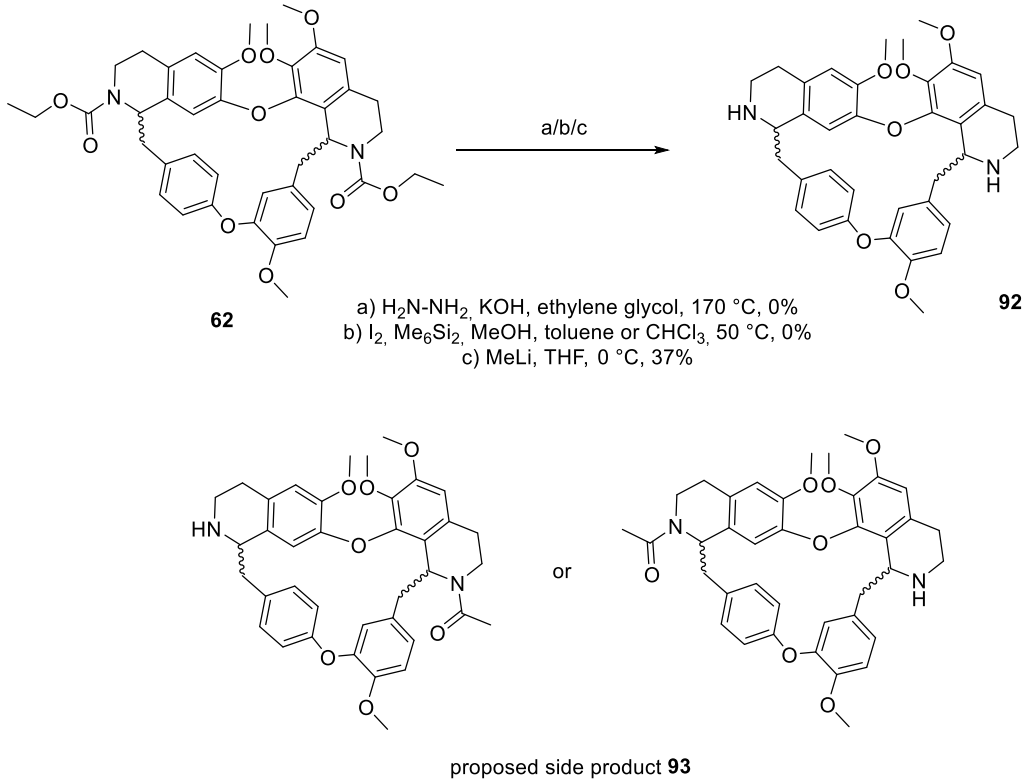
Table 7. Yields of bisbenzylisoquinoline compounds **RMS1**-**RMS6** and **RMS9**-**RMS10** after the reduction of the carbamate precursors **86**-**89** and **91**. *the stereoconfiguration of the butylidene intermediates **RMS9**-**RMS10** could not be determined.

entry	**carbamate intermediate**	**product**	**yield** (%) (*S,R*)/(*R,S*)	(*S,S*)/(*R,R*)
1	**86**		91 **RMS1**	94 **RMS2**

2	**87**		87 **RMS3**	74 **RMS4**
3	**89**		62 **RMS5**	77 **RMS6**
4	**91**		89* **RMS9**	70* **RMS10**

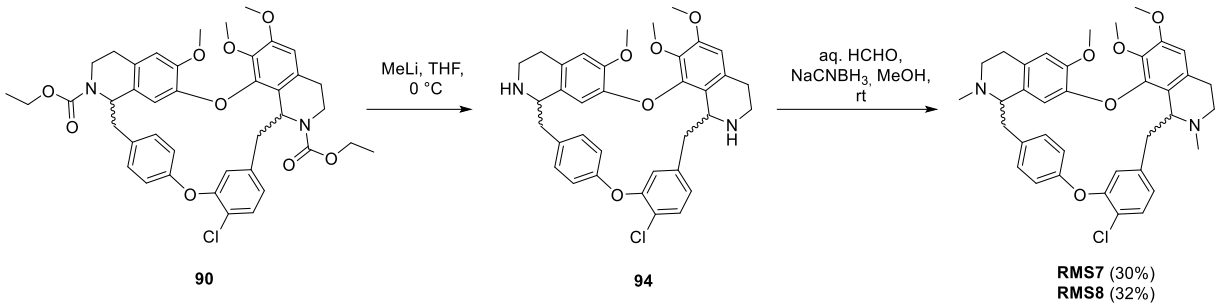
Only for the chloroarene variation **RMS7**/**RMS8** this method could not be applied, as it led to substantial dechlorination, even when the reaction was carried out at a lower temperature (ambient temperature instead of 50 °C) or when using the milder reduction reagent Red-Al® (sodium bis(2-methoxyethoxy)aluminium dihydride). As an alternative approach the carbamate groups should be first removed to give the secondary amino groups (N-2-*H*, N-2'-*H*) followed by *N*-methylation *via* reductive alkylation in a second step. To explore suitable reaction conditions compound **62** (an intermediate of the (iso)tetrandrine synthesis) was employed as model substrate (Scheme **24**). In a first attempt carbamate **62** was submitted to alkaline hydrolysis using KOH as base in ethylene glycol at 170 °C in the presence of hydrazine[136]. Neither upon conventional heating nor under microwave irradiation any traces of desired product could be detected by TLC-MS or ASAP analysis. Next, trimethylsilyl iodide (*in situ* generated with elemental iodine and hexamethyldisilane) was employed[137]. Since this method is also applied for the cleavage of ethers[138] side products resulting from desalkylation of the methoxy groups are to be expected, but were not observed (*via* TLC-MS/ASAP analysis). Unfortunately this method did not lead to the desired secondary amine **92** as well. A fast method was found using methyllithium[139], in which the starting material was completely

consumed within 1.5 h. In TLC-MS and ASAP analysis the mass of desired product **92** was detected, but a notable amount of a side product with the mass m/z 637 was also observed. Although this side product was not isolated and characterized, the mass peak could be assigned to a corresponding mono-amide **93** (depicted in Scheme **24**) as a result of incomplete reaction. Whereas a prolonged reaction time or elevated temperatures (ambient temperature instead of 0 °C) did not lead to a full conversion, the reaction completed after an increase of the amount of methyllithium from 6 to 10 equivalents. After the laborious isolation by FCC the desired product was obtained in a yield of 37%.



Scheme 24. Screening for reaction conditions for the conversion of the carbamate groups into secondary amines using intermediate **62** as model substrate.

With a protocol in hand for the cleavage of the carbamate groups this method was now successfully applied on the chloroarene intermediate **90**. Gratefully no side product resulting from dechlorination was observed in this approach. It was important that the temperature was kept at 0 °C, since above approximately 5 °C a degradation of the starting material occurred. It was found benefical to further increase the amount of methyllithium to 15 equivalents. Without purification the crude secondary amine **94** was then *N*-methylated using formaldehyde/$NaBH_3CN$ and the compounds **RMS7** and **RMS8** were obtained in almost identical yields of 30 and 32% over two steps (Scheme **25**).



Scheme 25. Cleavage of the carbamate groups of intermediate **90** and subsequent *N*-methylation.

As discussed before, the *N*-acyl Pictet-Spengler condensation proceeds almost racemic. Consequently, a mixture of diastereomers was generated accordingly in every variant. A separation of the obtained *seco*-bisbenzylisoquinolines **80**-**85** was possible by flash column chromatography. The bisbenzylisoquinolines **RMS1**-**RMS10** could be therefore eventually obtained as racemic compounds with the relative stereoconfiguration of either tetrandrine (*rac*-**1**) or isotetrandrine (*rac*-**2**) (see Figure **1**) in high diastereomeric ratios (d.r., determined by HPLC).

The relative stereochemistry of compounds **RMS1**-**RMS8** was determined *via* their NMR spectra according to the spectral characteristics of bisbenzylisoquinolines elaborated by Guinaudeau *et al*.[140]. In this study the NMR spectra of more than 100 bisbenzylisoquinolines were investigated and it was observed that the chemical shifts of distinctive protons in the ^{1}H-NMR spectra of bisbenzylisoquinolines correlate with the configuration of the asymmetric centres. Hereby the aromatic proton at C-10 resonates around *δ* (ppm) = 6.45 – 6.60 in the tetrandrine-type alkaloids (*R*,*R*)/(*S*,*S*) and further upfield around *δ* (ppm) = 6.20 – 6.45 in the isotetrandrine-type (*R*,*S*)/(*S*,*R*). There is an opposite trend for the signal of H-10', which is to be expected around *δ* (ppm) = 6.40 for the isotetrandrine-type and more upfield around *δ* (ppm) = 6.25 for the tetrandrine-type. The same applies to the singlet of the 6'-methoxy group that appears at around *δ* (ppm) = 3.60 in the (*R*,*S*)/(*S*,*R*) isomers and between *δ* (ppm) = 3.20 – 3.40 in the (*R*,*R*)/(*S*,*S*) isomers. In Table **8** the diagnostic chemical shifts of the synthetic bisbenzylisoquinolines **RMS1**-**RMS8** are summarized compared to the natural bisbenzylisoquinolines alkaloids tetrandrine (**1**) and isotetrandrine (**2**). Although the indicative signals of H-10, H-10' and 6'-OCH_3 are not always within the range described for tetrandrine- and isotetrandrine-like bisbenzylisoquinolines, they follow the trend found for tetrandrine (**1**) and isotetrandrine (**2**), respectively.

Table 8. Chemical shifts in the ^{1}H NMR spectra of bisbenzylisoquinolines of the tetrandrine- and isotetrandrine-type that indicate the relative stereochemistry of the alkaloids according to Guinaudeau *et al*.[140] *the signals of H-10 and H-10' overlap.

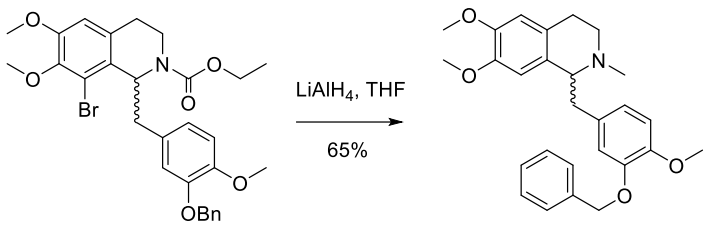
alkaloid	chemical shift [δ (ppm)]			relative stereoconfiguration	
	H-10	H-10'	6'-OCH_3	(*R*,*R*)/(*S*,*S*)	(*R*,*S*)/(*S*,*R*)
tetrandrine-type	6.45 – 6.60	~ 6.25	3.20 – 3.40	x	
isotetrandrine-type	6.20 – 6.45	~ 6.40	~ 3.60		x
tetrandrine (**1**)	6.55	6.30	3.37	x	
isotetrandrine (**2**)	6.48 – 6.37*	6.48 – 6.37*	3.61		x
RMS1	6.45 – 6.37*	6.45 – 6.37*	3.60		x
RMS2	6.55	6.30 – 6.28	3.37	x	
RMS3	6.64 – 6.57	6.45	3.60		x
RMS4	6.63	6.32 – 6.28	3.38	x	
RMS5	6.02	6.48 – 6.43	3.52		x
RMS6	6.24	6.26	3.36	x	
RMS7	6.54	6.44	3.61		x
RMS8	6.59	6.30	3.37	x	

Once the relative configurations were determined for the final compounds **RMS1**-**RMS8**, the stereochemistry of the corresponding (*seco*-)precursors was then assigned retrospectively. For the variations **RMS9**/**RMS10**, which contain an alkyl chain instead of the aromatic ring C, this method cannot be applied. Unfortunately this variant as free base or as hydrochloride salt resisted attempts of crystallization for the determination of the stereoconfiguration by crystallographic analysis. The relative stereochemistry of **RMS9**/**RMS10** as well as the corresponding precursors is therefore not specified.

3.3 SYNTHESIS OF *SECO*-ANALOGUES

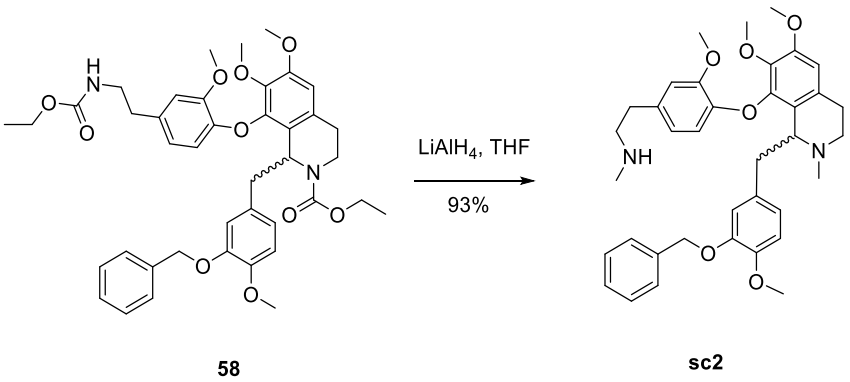
The synthesis of a small series of open-chain analogues of tetrandrine (**1**) is described in the following. Using an appropriately substituted 1-benzyltetrahydroisoquinoline as building block, the targeted variants represent truncated compounds gradually resembling tetrandrine (**1**) in their structure, as their complexity increases starting from the simple monomeric benzyltetrahydroisoquinoline **sc1** to the tetrahydroisoquinoline-benzyltetrahydroisoquinoline variants **sc4** and **sc5**. Apart from the benzylisoquinoline unit, all variations contain an *O*-benzyl residue, which is mimicking the aromatic ring C of the lead structure.

The monomeric 1-benzyltetrahydroisoquinoline **sc1** was directly synthesized from the intermediate **55** of the (iso)tetrandrine synthesis by lithium alanate reduction to the corresponding *N*-methylated compound. Following the established protocol, the carbamate moiety was readily reduced and the aryl bromide was cleaved simultaneously, as this method led to substantial debromination (Scheme **26**).



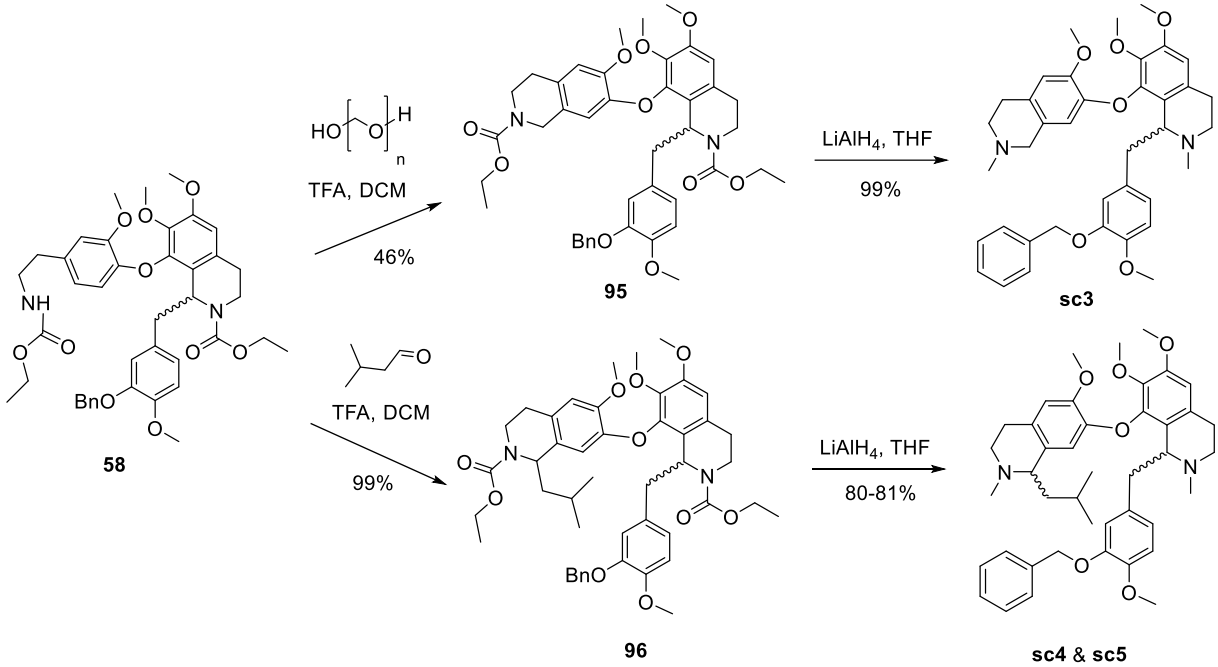
Scheme 26. Synthesis of **sc1** *via* reduction and debromination of the intermediate **55** with lithium alanate.

For the synthesis of *seco*-analogues **sc2**-**sc5** the intermediate **58** of route 1a of the (iso)tetrandrine synthesis was used as starting material. Reduction of the carbamate groups in **55** using lithium alanate, gave the *N*-methylated secondary amine **sc2** (Scheme **27**) in a yield of 93%.



Scheme 27. Synthesis of *seco*-intermediate **sc2** by reduction of intermediate **58** to the secondary amine.

The TFA-catalyzed *N*-acyl Pictet-Spengler condensation of **58** with paraformaldehyde furnished intermediate **95** (Scheme **28**) in 46% yield.



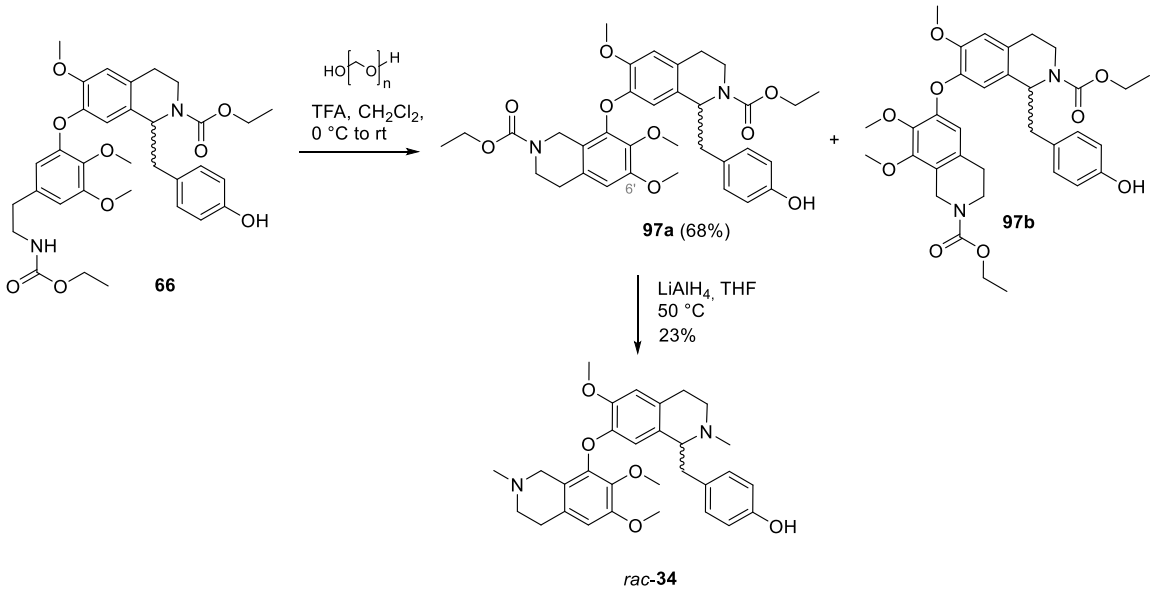
Scheme 28. Synthesis of *seco*-intermediates **sc3**-**sc5**. TFA-catalyzed *N*-acyl Pictet-Spengler reactions with intermediate **58** and subsequent carbamate reductions of the intermediates **95**-**96** gave *N*-methylated *seco*-analogues **sc3**-**sc5**.

Reacting **58** with 3-methylbutyraldehyde following the standard protocol of the *inter*molecular *N*-acyl Pictet-Spengler yielded almost quantitatively intermediate **96** as an equimolar mixture of racemic diastereomers (Scheme **28**), which were readily separable by flash column chromatography. The *N*-acyl Pictet-Spengler reaction in this step proceeded in a regioselective manner and delivered exclusively the desired isomers, which was confirmed by NMR analysis (HMBC). Subsequent reduction of **95** and **96** with $LiAlH_4$ gave the isoquinoline-benzylisoquinoline *seco*-compounds **sc3**-**sc5** in good to excellent yields (80-99%). The determination of the relative stereochemistry of **sc4** and **sc5** was attempted by NMR analysis. The asymmetric centres in **sc4** and **sc5** bear bulky residues such as the isobutyl and the benzyl group, which have – depending on their relative stereochemistry – a different spatial orientation to each other. This might be detectable by NOESY analysis, but unfortunately the NOESY spectra of both diastereomers were too similar for any differentiation. Next, crystallization was attempted for crystallographic analysis of the diastereomers, but unfortunately neither **sc4** nor **sc5** (as free bases) gave crystals in a sufficient quality. Also after conversion into the hydrochloride salts cristalization was unsuccesful. The stereoconfiguration of **sc4** and **sc5** and the corresponding precursors (**96**) is therefore not further specified.

3.4 SYNTHESIS OF RELATED ALKALOIDS

3.4.1 MURARICINE

As aforementioned the carbamate **66**, which is an intermediate of route 1b of the tetrandrine synthesis (see chapter **3.1**) served as starting material for the synthesis of racemic muraricine (*rac*-**34**). Building block **66** was reacted in an *N*-acyl Pictet-Spengler condensation with paraformaldehyde to give the muraricine precursor **97a** (Scheme **29**). As already observed in the synthesis of (iso)tetrandrine and respective analogues, again a side product with the identical mass could be detected, which is most plausibly the regioisomer **97b**. The product ratio **97a**:**97b** amounted 69:31, as determined by HPLC. To minimize the formation of the undesired regioisomer **97b** a solvent-directed approach[131, 141] was applied, similarly as already examined in the synthesis of tetrandrine (**1**). According to the protocol of Kayhan *et al.*[131], the *N*-acyl Pictet-Spengler condensation was carried out in the more polar solvent methanol, which should preferentially lead to a cyclization in *para*-position to the 6'-methoxy group. Unfortunately the reaction proceeded very slowly and incomplete under these conditions, just as observed in the synthesis of tetrandrine (**1**), when conducting this step in trifluoroethanol instead of DCM as usual. But luckily also in this case the desired isomer **97a** could be separated from **97b** and was isolated in a yield of 68% by flash column chromatography. For the unambiguous identification of regioisomer **97a** 2D NMR experiments were performed. With HMBC experiments of **97a** and NOESY experiments of *rac*-**34** respectively, the structure of **97a** could be verified. In the last step bis-carbamate **97a** was reduced with $LiAlH_4$ to furnish racemic muraricine (*rac*-**34**) in 23% yield. The NMR data of synthetic racemic muraricine (*rac*-**34**) were in accordance with the data of the natural alkaloid **34** isolated from *Berberis vulgaris* by Host'álková *et al*.[119].

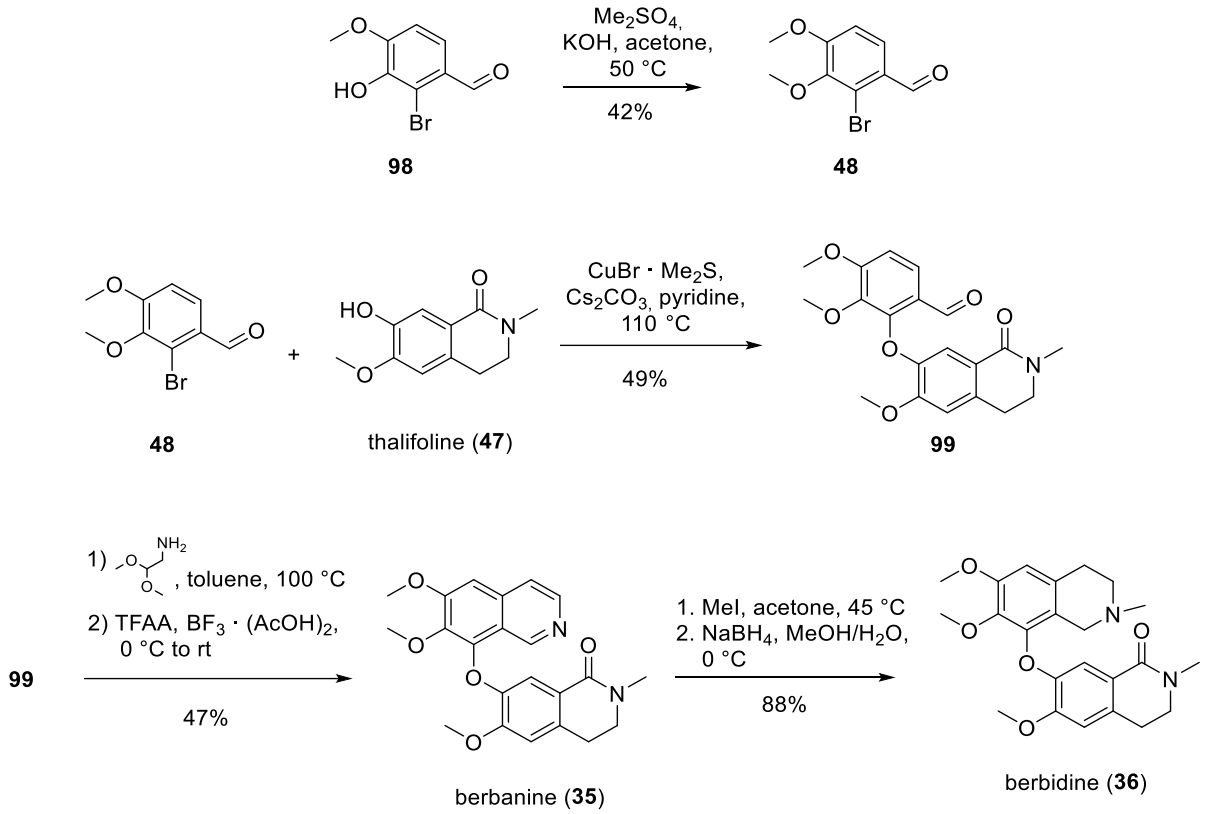


Scheme 29. Synthesis of racemic muraricine (*rac*-**34**).

3.4.2 BERBANINE AND BERBIDINE

For the synthesis of the dimeric isoquinoline-isoquinolone alkaloids berbanine (**35**) and berbidine (**36**) the 1-oxodihydroisoquinoline thalifoline (**47**) was used as building block. Thalifoline (**47**) was synthesized by Sandra Schmidt as part of her master's thesis according to a newly developed protocol for 1-oxodihydroisoquinoline alkaloids[120]. To access the diaryl ether moiety phenolic compound **47** was reacted with 2-bromo-3,4-dimethoxybenzaldehyde (**48**) following the established protocol already used in the synthesis of (iso)tetrandrine. Bromoarene **48** was synthesized in one step from commercially available 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**98**) *via O*-methylation with Me_2SO_4[142]. The Ullmann-type coupling furnished the diaryl ether **99** in a yield of 49%. Intermediate **99** was then further processed in a Pomeranz-Fritsch reaction using aminoacetaldehyde dimethylacetal and boron trifluoride/acetic acid complex as Lewis acid applying the conditions published by Patel for the synthesis of related isoquinolines[143] to obtain the alkaloid berbanine (**35**) in 47% yield. Surprisingly, the NMR data of synthetic berbanine (**35**) were not in accordance with the data of isolated berbanine published by Host'álková *et al*.[144]. Apart from several deviations of chemical shifts in the ^{1}H and ^{13}C NMR spectra, most striking was a deviation in the signal of proton 1'-H of the isoquinoline moiety. Host'álková *et al*. report a doublet at 9.23 ppm (J = 5.9 Hz), whereas a singlet further upfield at 9.16 ppm was found for synthetic berbanine. A reasonable explanation for the downfield shift and multiplicity of the 1'-H signal in Host'álková's data might be that not the free base was characterized as reported, but the protonated isoquinolinium species of **35**. After the conversion of synthetic berbanine into its hydrochloride salt, the NMR data thereof was largely identical with the reported data of the isolated alkaloid.

Next, berbanine (**35**) was converted into its *N*-methylated 1,2,3,4-tetrahydro analogue berbidine (**36**) in two steps following a method of Chan *et al*.[145]. *N*-Methylation of the aromatic isoquinoline **35** using methyl iodide gave an isoquinolinium salt, which was reduced with sodium borohydride to furnish alkaloid **36** in a yield of 88% over two steps (Scheme **30**).



Scheme 30. Synthesis of the alkaloids berbanine (**35**) and berbidine (**36**).

4 PHARMACOLOGICAL EVALUATION

As mentioned above several biological activities such as anticancer, antiviral, chemoresistance reversing and calcium channel blocking properties are known for tetrandrine (**1**). The synthesized (iso)tetrandrine analogues **RMS1**-**RMS10**, the *seco*-analogues **sc1**-**sc5** and racemic muraricine (*rac*-**34**) were subjected to pharmacological characterization with a focus on antitumoral activities. These compounds were therefore screened for their antiproliferative and multidrug resistance reversing activity. Moreover the substances were investigated for their toxicity as the reduction of tetrandrine's (**1**) toxic effects is of central interest. Additionally, MTT and standard agar diffusion assays were employed as part of an in-house routine screening for assessing cytotoxicity and antimicrobial activity, respectively. The screenings for antiproliferative and multidrug resistance reversing activity as well as toxicological evaluation were performed by Martin Müller and Franz Geisslinger of the group of Prof. Dr. Angelika Vollmar (chair of pharmaceutical biology, LMU Munich). The MTT and agar diffusion assays were performed by Martina Stadler of our group. The results were already published in ref. 53 (tetrandrine analogues **RMS1**-**RMS10**) and ref. 122 (*rac*-**34**). The *seco*-analogues **sc1**-**sc5** were pharmacologically characterized by Franz Geisslinger within the scope of his master's thesis[146].

4.1 ANTIPROLIFERATIVE ACTIVITY

The effect of the (iso)tetrandrine analogues **RMS1**-**RMS10** and the *seco*-analogues **sc1**-**sc5** on cell proliferation was assessed using vincristine-resistant cells (VCR-R CEM cells). VCR-R CEM cells are P-gp overexpressing leukemia cells that are cross-resistant to a variety of cytostatic agents[147]. VCR-R CEM cells were treated with increasing concentrations (0.01 – 50 µM) of the test compounds and cell viability was determined 48 h after exposure to the compounds employing a CellTiter-Blue® cell viability assay. Table **9** summarizes the IC_{50} values of the tested compounds compared to natural tetrandrine (**1**, isolated from natural sources and kindly donated by Prof. Dr. Peter Pachaly).

Table 9. Antiproliferative activity of (iso)tetrandrine analogues **RMS1**-**RMS10** and *seco*-analogues **sc1**-**sc5** assessed on VCR-R CEM cells. The experiments were performed in triplicates.

compound	IC_{50} [µM]	compound	IC_{50} [µM]
tetrandrine (**1**)	15.8		
(iso)tetrandrine analogues		*seco*-analogues	
RMS1	4.8	**sc1**	> 50
RMS2	4.4	**sc2**	> 50
RMS3	3.8	**sc3**	12
RMS4	4.2	**sc4**	8.9
RMS5	7.1	**sc5**	7.5
RMS6	> 50		
RMS7	4.9		
RMS8	4.8		
RMS9	> 50		
RMS10	> 50		

Compared to the lead structure tetrandrine (**1**), the analogues **RMS1**-**RMS5**, **RMS7**-**RMS8** and the *seco*-compounds **sc3**-**sc5** showed an increased antiproliferative activity against VCR-R leukemia cells. Six of the macrocyclic analogues (**RMS1**-**RMS4**, **RMS7**-**RMS8**) were three to four times more potent than tetrandrine (**1**). The propylidene analogues containing an alkyl residue instead of the aromatic ring C (**RMS9**-**RMS10**), as well as the thiophene analogue with the relative stereochemistry of tetrandrine (*R*,*R*/*S*,*S*) (**RMS6**) were nearly inactive. Surprisingly its diastereomer **RMS5** did show an antiproliferative effect, although weaker than the other active analogues. Except for the diastereomeric compounds **RMS5** and **RMS6**, no relevant difference in the antiproliferative potency of diastereomers can be observed. The *seco*-

analogues **sc1** and **sc2**, which are lacking a second tetrahydroisoquinoline moiety (ring B'), were also inactive.

The synthetic isoquinoline-benzylisoquinoline alkaloid muraricine (*rac*-**34**) was also screened for antiproliferative activity using hepatocellular carcinoma (HepG2), colorectal adenocarcinoma (HCT-15), and bladder carcinoma (T24) cell lines. The cells were incubated with increasing concentrations of *rac*-**34** or tetrandrine (**1**) (0.1 – 50 µM) for 72 h and cell viability was determined by CellTiter-Blue® assay. No cytotoxic activity and only very low antiproliferative effects were observed, when compared to tetrandrine (**1**). Consequently, muraricine (*rac*-**34**) does not possess a direct anticancer activity. The data is shown as supplementary material on Figure **22** (chapter **7.1**).

In terms of structure-activity relationship this data indicates that the aromatic ring C and the presence of two tetrahydroisoquinoline units might be important structural elements for antiproliferative activity. Moreover, the antiproliferative properties seem to be mainly independent of the relative stereochemistry. This needs to be further investigated in SAR studies involving a larger number of structure variations, for which these findings provide a first basis and give inspiration for the design of new variants.

4.2 P-GP INHIBITION

The inhibitory effects of the (iso)tetrandrine analogues **RMS1**-**RMS10**, the *seco*-analogues **sc1**-**sc5** and racemic muraricine (*rac*-**34**) on the efflux pump P-gp were investigated in VCR-R CEM cells, the same cell line which was used for assessing antiproliferative effects. Owing to the overexpression of P-gp VCR-R CEM cells are a suitable model for the investigation of P-gp inhibition. Hereby the effect of the analogues on P-gp was assessed in two assays. In a calcein-AM retention assay[52] the direct interaction with the multidrug resistance transporter was determined and, in a subsequent Nicoletti assay[148], the cells were treated with the cytostatic agent and P-gp substrate vincristine (VCR) in combination with the tested compounds. An increase in vincristine susceptibility indicates a reversal of multidrug resistance.

In the calcein-AM retention assay a model substrate of P-gp, calcein-AM, the nonfluorescent acetoxymethyl ester of the fluorescent dye calcein, accumulates in cytoplasmatic compartments, if P-gp is inhibited. Calcein-AM is then cleaved by cellular esterases to calcein, which results in an increase of fluorescence intensities. In this assay, the cells were incubated with the tested compounds in increasing concentrations and calcein-AM (200 nM) for 30 min. The cells were then washed to remove excess calcein-AM and again incubated with the potential P-gp inhibitor for 1 h. Lastly, calcein fluorescence was determined by flow cytometry. The *seco*-analogues **sc1**-**sc5** were tested at 0.1, 1 and 10 µM, as these concentrations were well tolerated by the cells. The compounds **RMS1**-**RMS10** could be tested only in concentrations up to 1 µM, since the cell viability was strongly affected at higher doses. Muraricine (*rac*-**34**) was assessed using the same protocol but in generally higher concentrations (1, 10, 20 and 50 µM) and the known second-generation P-gp inhibitor verapamil (**8**) was used as a positive control. Verapamil (**8**) was a suitable positive control for muraricine (*rac*-**34**), since the cells tolerated high micromolar concentrations of the compound (≤ 50 µM).

All full (iso)tetrandrine analogues, except the propylidene analogues **RMS9**-**RMS10**, were able to inhibit P-gp to a similar extent as tetrandrine (**1**) (Figure **13**, **A**). Among the *seco*-analogues **sc4** and **sc5** exhibited inhibitory activity (Figure **13**, **B**), which was similar compared to that of tetrandrine (**1**). Compounds **sc1**-**sc3** as the least active substances showed no noteworthy inhibition below 10 µM. To test whether an improved P-gp inhibition can be achieved by dose increase, muraricine (*rac*-**34**) was exemplarily employed at higher concentrations (≤ 50 µM), at which the alkaloid had only marginal antiproliferative effects. Muraricine (*rac*-**34**) did not show any activity in concentrations below 10 µM, but in higher concentrations (10-50 µM) a dose-dependent inhibition of calcein efflux could be detected (Figure **13**, **C**).

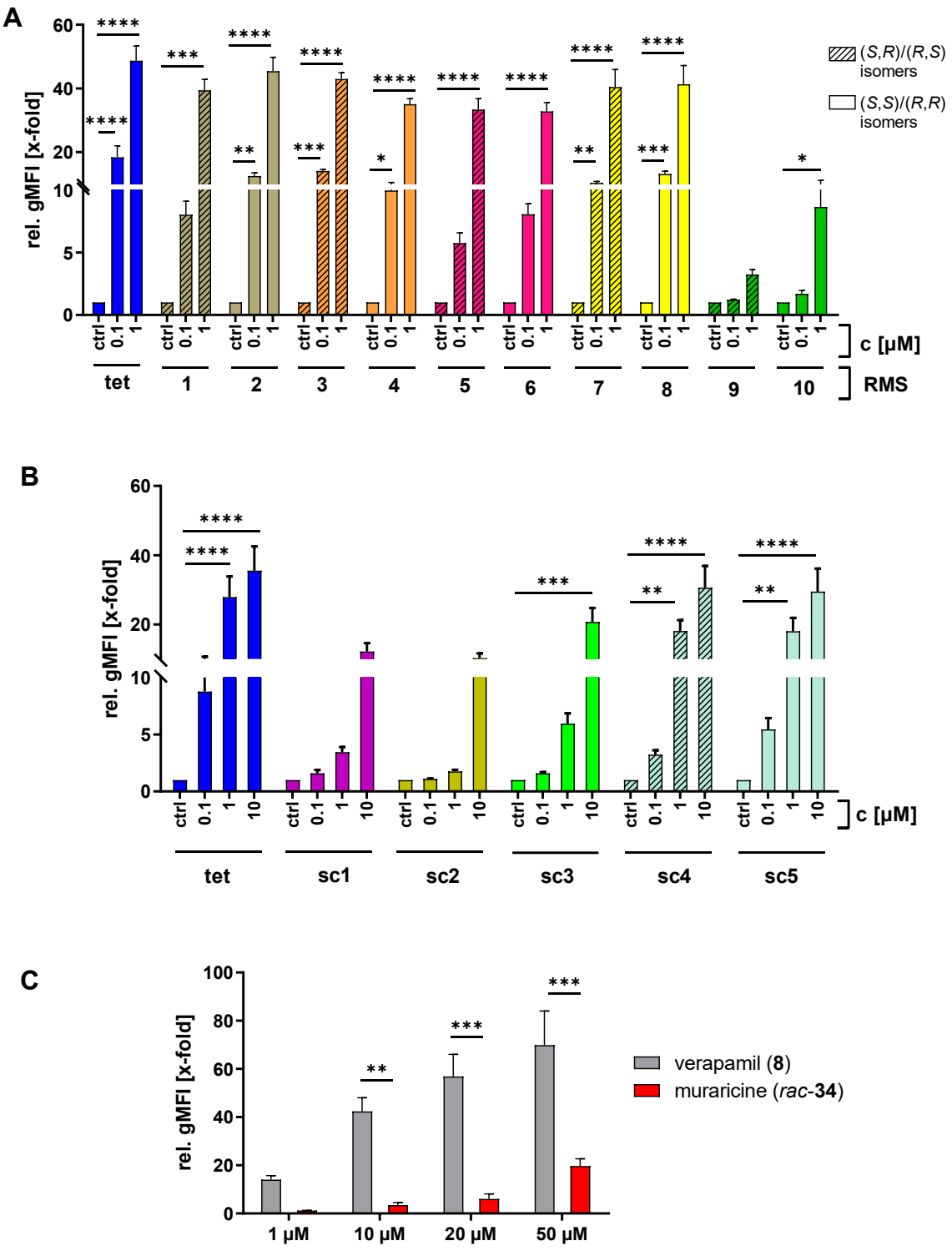
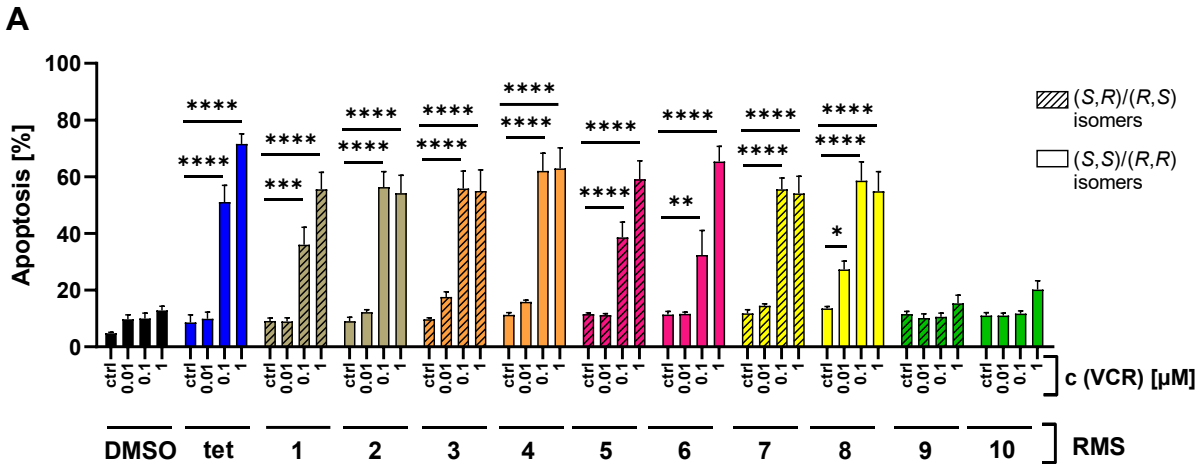


Figure 13. Inhibition of P-gp-mediated calcein-AM efflux determined by calcein retention assay in VCR-R CEM cells. (**A**) Inhibition of P-gp by treatment with **RMS1**-**RMS10** and tetrandrine (**1**). (**B**) Treatment with *seco*-analogues **sc1**-**sc5** and tetrandrine (**1**). (**C**) Treatment with racemic muraricine (*rac*-**34**) and verapamil (**8**). Ctrl: solvent control, tet: tetrandrine (**1**). Geometric means of fluorescence intensities (gMFI) of treated samples were normalized to the untreated calcein-AM control. Bar graph indicates means ± SEM of three independent experiments (**A**,**B**: two-way ANOVA followed by Dunnett's multiple comparison test, **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001; **C**: one-way ANOVA followed by Tukey's multiple comparison test, ***P* < 0.01, ****P* < 0.001).

Next, the cells were treated with increasing concentrations of vincristine (VCR) (0.01, 0.1 and 1 µM) in combination with the tested compounds in a specified concentration of 1 µM. Only muraricine (*rac*-**34**) was used in a higher concentration of 25 µM in combination with 0.1 or 1 µM of vincristine. After an incubation time of 48 h the percentage of apoptotic cells was determined *via* propidium iodide (PI) staining and flow cytometry (Nicoletti assay). Propidium iodide staining is performed in a hypotonic buffer, enabling the PI to bind and label DNA and to quantify apoptotic, hypodiploid cells[148].

Again, all macrocyclic analogues except **RMS9**-**RMS10** were able to resensitize VCR-R CEM cells to the vincristine treatment by inhibiting P-gp as evident by strongly increased apoptosis rates at 0.1 and 1 µM of vincristine (Figure **14**, **A**). Very similar to the observations made in the calcein-AM retention assay, the *seco*-analogues **sc4** and **sc5** were the most active substances among the *seco*-series in reversing multidrug resistance similar to tetrandrine (**1**). As expected **sc2** and **sc3** did not increase apoptosis rates at 1 µM, **sc1** suprisingly showed weak activity in combination with 1 µM of VCR (Figure **14**, **B**). Muraricine (*rac*-**34**), employed at a concentration of 25 µM, markedly led to an increase of apoptosis in the combination treatment with vincristine in 0.1 and 1 µM concentration (Figure **14**, **C**). As observed for the antiproliferative effects, the relative stereochemistry of the compounds is not an important factor for the chemoresistance reversing activity as well.



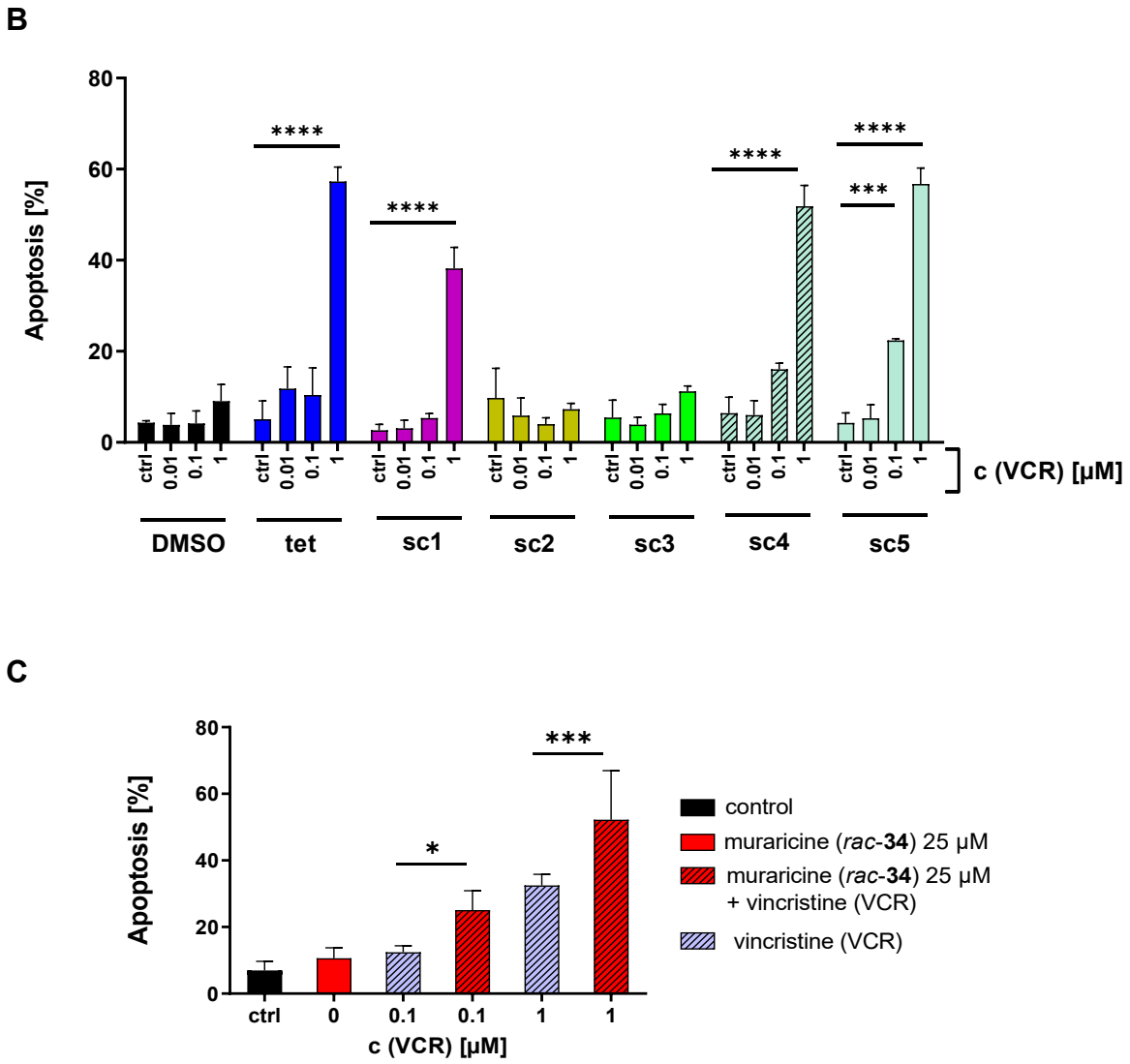


Figure 14. Combination treatment of chemoresistant VCR-R CEM cells. (**A**) Vincristine (VCR) and **RMS1**-**RMS10** or tetrandrine (**1**). (**B**) Vincristine (VCR) and *seco*-analogues **sc1**-**sc5** or tetrandrine (**1**). (**C**) Vincristine (VCR) and racemic muraricine (*rac*-**34**). Ctrl: solvent control, tet: tetrandrine (**1**). Bar graph indicates means ± SEM of three independent experiments (**A**,**B**: two-way ANOVA followed by Dunnett's multiple comparison test, **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001); **C**: one-way ANOVA followed by Tukey's multiple comparison test, **P* < 0.05, ****P* < 0.001).

4.3 TOXICITY

The toxicity of the macrocyclic (iso)tetrandrine analogues **RMS1**-**RMS10** and the *seco*-derivatives **sc1**-**sc5** was evaluated in several cancerous and non-malignant cell lines.

As the variations **RMS1**-**RMS10** were designed to be less toxic than the lead structure tetrandrine (**1**), the evaluation of their toxicity was of central interest. The compounds **RMS1**-**RMS10** are lacking the hypothesized metabolically instable methoxy group at C-12, which is discussed to undergo a CYP-mediated oxidative metabolism resulting in a potentially toxic quinone methide intermediate[55]. Beside the assessment of general toxicity, it should be specifically investigated whether the CYP3A4-driven metabolism is in fact the major mechanism of tetrandrine-induced toxicity. For this purpose, two cell lines were employed, the non-malignant HepaRG™ cells and the liver cancer cell line HepG2. HepaRG™ is a hepatic cell system frequently used to study drug metabolism and hepatotoxicity as these cells possess several characteristics of human hepatocytes such as the expression of P450 enzymes[149-150], including CYP3A4. HepaRG™ cells were treated with the analogues **RMS1**-**RMS10** and tetrandrine (**1**) at 10 and 20 µM (Figure **15**, **A**). After an incubation time of 24 h, cell viability was determined *via* CellTiter-Blue® cell viability assay. Surprisingly, none of the analogues was significantly less toxic to HepaRG™ cells than the lead structure tetrandrine (**1**) at 10 µM, only at the higher concentration of 20 µM a decreased toxicity was observed for **RMS6** and **RMS9** compared to tetrandrine (**1**). Unlike expected the compounds **RMS2**, **RMS4** and **RMS8** exhibited even increased toxic effects, whereas the toxicity of all other analogues was similar to that of tetrandrine (**1**) at both concentrations.

As the hypothesized metabolic pathway requires CYP3A4 enzymatic activity to transform tetrandrine (**1**) into the putatively toxic *para*-quinone methide, it was additionally investigated whether an overexpression of CYP3A4 would further enhance the compounds' toxicity. Therefore, HepaRG™ cells were transiently transfected with a vector coding for CYP3A4 (pcDNA3-CYP3A4-EGFP) or an empty vector control. The treatment of CYP3A4 overexpressing cells with compounds **RMS1**-**RMS10** or tetrandrine (**1**) (10 µM, 24 h) did not lead to a considerable increase of cell death compared to the treatment of control HepaRG™ cells (Figure **15**, **B**) transfected with the empty vector.

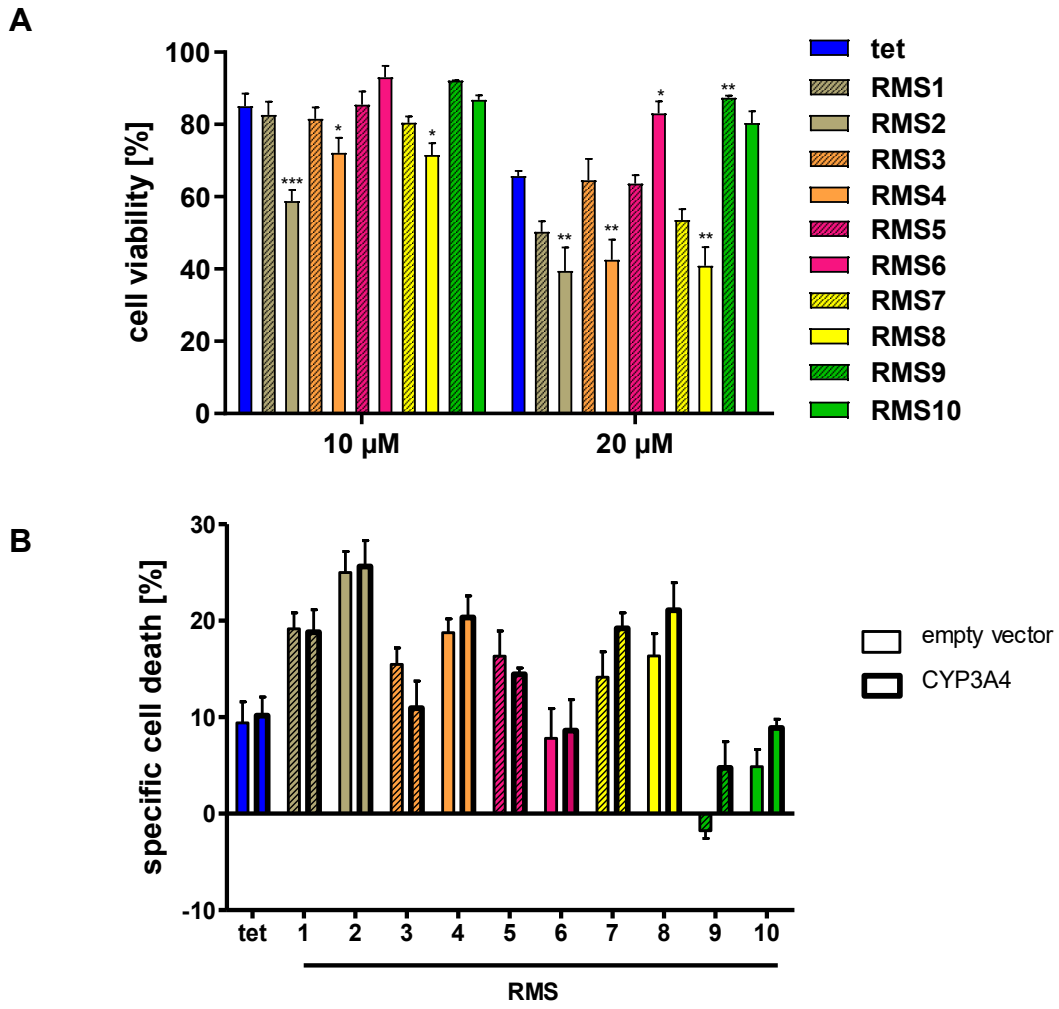


Figure 15. Toxicity assessment of **RMS1**-**RMS10** and tetrandrine (**1**) in HepaRG™ cells. (**A**) Differentiated HepaRG™ cells treated with 10 and 20 µM of **RMS1**-**RMS10** or tetrandrine (**1**). (**B**) CYP3A4 overexpressing (thick bars) or control (thin bars) HepaRG™ cells with 10 µM of **RMS1**-**RMS10** or tetrandrine (**1**). Tet: tetrandrine (**1**). Bar graph indicates means ± SEM of three independent experiments (**A**: one-way ANOVA followed by Dunnett's multiple comparison test, relative cell viabilites were compared with that of tetrandrine (**1**), **P* < 0.05, ***P* < 0.01, ****P* < 0.001; **B**: unpaired t-test with Welch's correction, not significant).

To further determine the influence of CYP3A4 activity on toxicity, the cancer cell line HepG2 (hepatocellular carcinoma cells) as an additional standard *in vitro* model for CYP metabolism studies, was employed. To facilitate overexpression of CYP3A4, HepG2 cells were stably transfected with a pcDNA3-CYP3A4-EGFP vector. Cells that were stably transfected with an empty vector served as control. Also in this cellular model, cytotoxic effects on CYP3A4 overexpressing cells and on control cells were very similar (Figure **16**). Consequently, cytotoxicity could again not be correlated to the level of cellular CYP3A4 expression. The majority of analogues (**RMS1**-**RMS5** and **RMS7**-**RMS8**) showed strongly enhanced cytotoxic effects compared to tetrandrine (**1**), as the specific cell death was twice as high. Only **RMS6**,

RMS9 and **RMS10** affected cell viability slightly less than or similarly to tetrandrine (**1**), as already observed in the HepaRG™ cells.

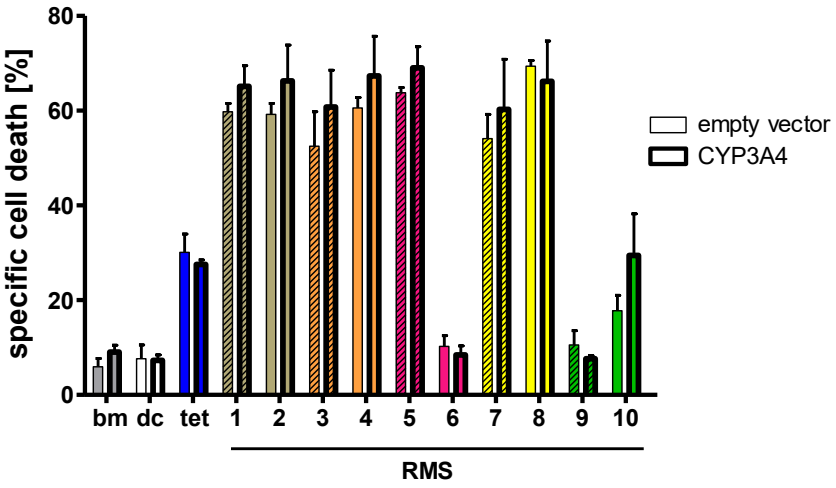


Figure 16. Toxicity assessment of **RMS1**-**RMS10**, berbamine (**100**), dauricine (**3**) and tetrandrine (**1**) in CYP3A4 overexpressing (thick bars) or control (thin bar) HepG2 cells with 15 µM of each compound (cells were treated for 24 h). Tet: tetrandrine (**1**), bm: berbamine (**100**), dc: dauricine (**3**). Bar graph indicates means ± SEM of three independent experiments (unpaired t-test with Welch's correction, not significant).

In the hypothesized metabolic pathway of tetrandrine (**1**), the first step is the demethylation of the methoxy group at C-12 prior to oxidation to the discussed quinone methide[55]. This *O*-demethylation process is catalyzed by not further specified CYP enzymes. Assuming that HepG2 cells are lacking these essential enzymes required for initial demethylation, the metabolism to the *para*-quinone methide might not occur. Consequently, this could explain the observed similar cytotoxic effects on both CYP3A4 overexpressing and control cells. To rule this out, the related bisbenzylisoquinoline alkaloids berbamine (**100**) and dauricine (**3**; a *seco*-bisbenzylisoquinoline) (see Figure **17**) that already bear a free phenol at C-12 instead of a methoxy group susceptible to direct oxidation by CYP3A4 enzymes, were also tested using HepG2 cells (Figure **16**). As observed for tetrandrine (**1**) and the analogues **RMS1**-**RMS10**, the cytotoxic effects were again independent of the expression level of CYP3A4.

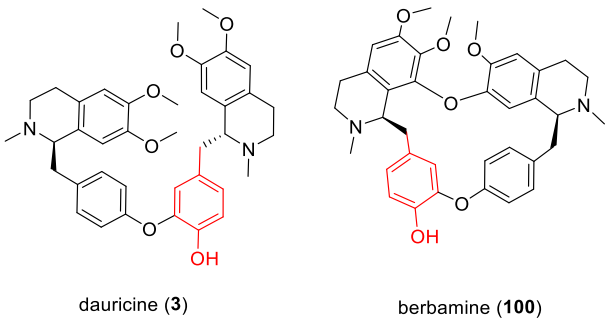


Figure 17. (*Seco*)bisbenzylisoquinoline alkaloids dauricine (**3**) and berbamine (**100**) with the *para*-hydroxybenzyl structure (highlighted in red) prone to oxidative metabolism.

Considering the anticancer properties in relation to toxic effects, **RMS3** and **RMS5** possess the most benefical pharmacological profile among the RMS series, as they exerted strongly enhanced antiproliferative and cytotoxic effects, MDR reversing activities similar to that of tetrandrine (**1**), whereas their toxic properties on HepaRG™ were not inferior compared to the lead structure. Although a decrease of toxicity could not be achieved directly, an indirect reduction of toxic effects by lowering required doses might be possible. To further analyse the toxicity of the highly active compounds **RMS3** and **RMS5**, additional studies with human umbilical vein endothelial cells (HUVECs) and peripheral blood mononuclear cells (PBMCs), both representing non-cancerous primary cell lines, were conducted. Both cell lines were treated with **RMS3**, **RMS5** or tetrandrine (**1**) at increasing concentrations (1, 5 and 10 µM) for either 48 h (PBMCs) or 24 h (HUVECs). Viability of HUVECs was determined *via* CellTiter-Blue® cell assay and cell death of PBMCs was quantified using flow cytometry after propidium iodide staining. In both cell lines the toxic effects of **RMS3** and **RMS5** were largely equal to those of tetrandrine (**1**). A slight difference was observed in PBMC cells treated with compounds at a concentration of 10 µM (Figure **18**, **A**). In this case tetrandrine (**1**) affected the cell viability most, as indicated by the high percentage of cell death. In contrast, **RMS3** at the same concentration (10 µM) showed slightly higher toxic effects on HUVEC cells compared to tetrandrine (**1**) (Figure **18**, **B**). Combining the data of all toxicity studies, no substantial difference in the cytotoxic potencies of the analogues **RMS3**/**RMS5** and tetrandrine (**1**) can be observed.

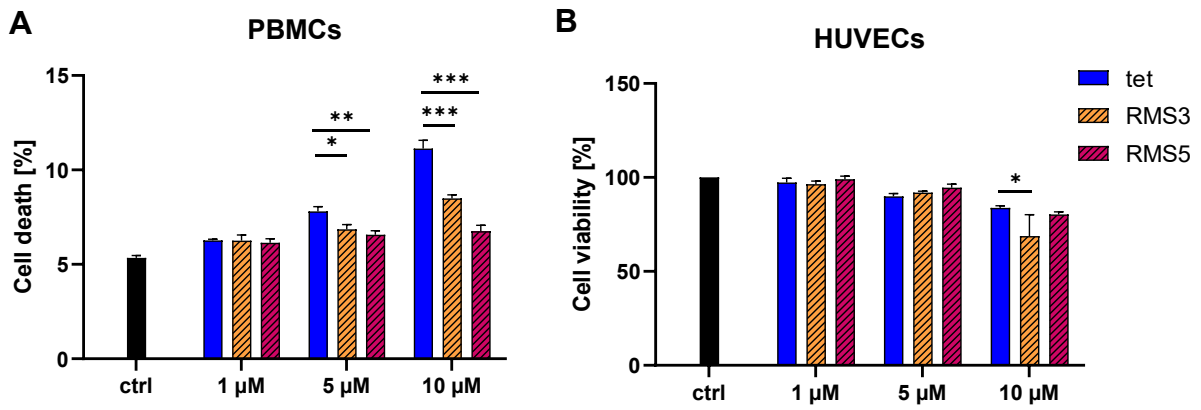


Figure 18. Toxicity assessment of **RMS3**, **RMS5** and tetrandrine (**1**) in (**A**) human umbilical vein endothelial cells (HUVECs) and (**B**) peripheral blood mononuclear cells (PBMCs). Ctrl: solvent control, tet: tetrandrine (**1**). Bar graph indicates means ± SEM of three independent experiments (two-way ANOVA followed by Dunnett's multiple comparison test, **P* < 0.05, ***P* < 0.01, ****P* < 0.001).

The acute toxicity of **sc1**-**sc5** was also determined using HUVEC and PBMC cells. Hereby, the assessment of general toxicity compared to tetrandrine (**1**) and not the metabolic pathway leading to potentially toxic intermediates was the primary objective. Like the lead structure tetrandrine (**1**), all *seco*-analogues **sc1**-**sc5** possess the *para*-methylene methoxy group at C-

12, that could potentially be *O*-demethylated and oxidized to the corresponding quinone methide. Similar to the previous section, the cells were treated with **sc1**-**sc5** or tetrandrine (**1**) at increasing concentrations (1, 5, 10 and 20 µM) for either 48 h (PBMCs) or 24 h (HUVECs) and the cell viability was determined as mentioned before. The cell viability of PBMCs is only slightly affected by the tested compounds in the low concentration range of 1-5 µM (Figure **19**, **A**). In higher concentrations of 10 and 20 µM cell death markedly increases upon treatment with **sc2**-**sc5** and tetrandrine (**1**), whereas **sc1** barely shows toxic effects (Figure **19**, **A**). On HUVEC cells **sc1** likewise had only a minor effect on cell viability in the tested concentration range, **sc2**-**sc4** showed toxic effects largely similar to tetrandrine (**1**) and **sc5** was the most toxic compound especially at higher concentrations (≥ 10 µM) (Figure **19**, **B**).

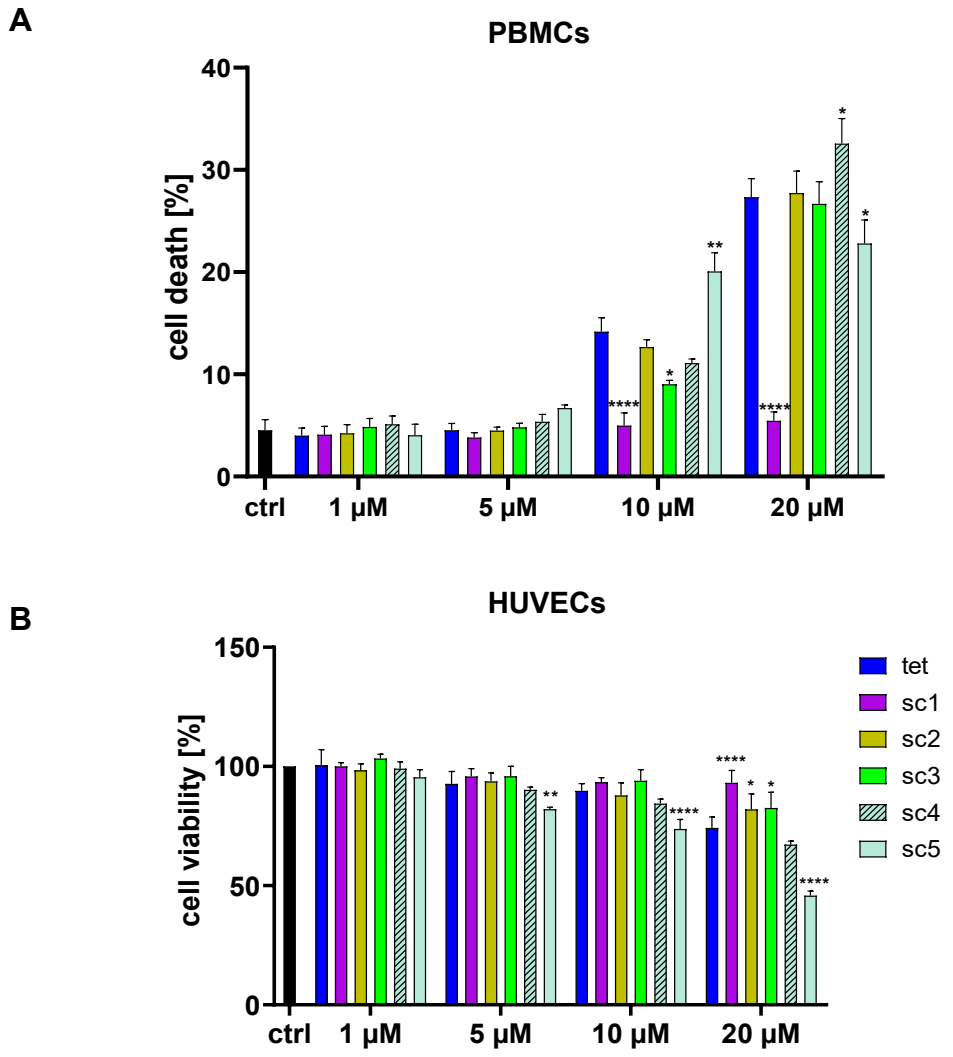


Figure 19. Toxicity assessment of the *seco*-analogues **sc1**-**sc5** and tetrandrine (**1**) in (**A**) PBMC cells and (**B**) HUVEC cells. Ctrl: solvent control, tet: tetrandrine (**1**). Bar graph indicates means ± SEM of three independent experiments (two-way ANOVA followed by Dunnett's multiple comparison test. The relative cell viabilites and the percentage of cell death were compared with that of tetrandrine (**1**) in the respective concentrations, **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001).

The toxicity assessment of racemic muraricine (*rac*-**34**) was determined using HUVEC cells as well. The cells were incubated with *rac*-**34** or tetrandrine (**1**) in increasing concentrations (10, 20 and 50 µM) for 6 h and the cell viability was measured using CellTiter-Glo® cell assay detecting the intracellular adenosine triphosphate (ATP) content as a surrogate of cell viability. Whereas tetrandrine (**1**) exhibited strong toxic effects on HUVEC cells, the cell viability was nearly unaffected when applying racemic muraricine (*rac*-**34**) in the tested concentration range (Figure **20**).

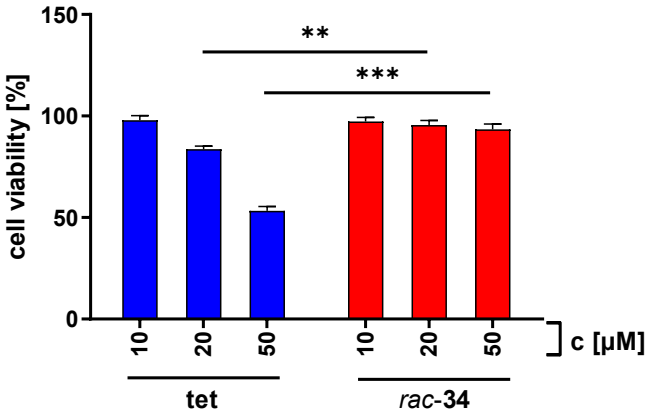


Figure 20. Toxicity assessment of racemic muraricine (*rac*-**34**) in HUVEC cells. Tet: tetrandrine (**1**), *rac*-**34**: racemic muraricine. Bar graph indicates means ± SEM of three independent experiments (one-way analysis of variance followed by Tukey's multiple comparison test; $^{**}p < .01$, $^{***}p < .001$).

Summarizing, with most of the structure variations that are present in **RMS1**-**RMS10** no considerable reduction of the toxicity of tetrandrine (**1**) could be achieved as shown by several *in vitro* models. Only the analogues **RMS6** and **RMS9** (**RMS10** slightly) showed decreased toxicity to some extent, whereas all other compounds did not substantially differ from tetrandrine (**1**) or exhibited even increased toxic effects. It has to be stated that a decrease of toxicity as observed for **RMS6**, **RMS9** and **RMS10** is unfortunately accompanied by a concurrent reduction of antitumoral activity. Moreover, the cytotoxic potency of tetrandrine (**1**) and the analogues **RMS1**-**RMS10** was mainly unaffected by the extent of cellular CYP3A4 expression. Therefore it can be concluded that the hypothesized CYP3A4-mediated metabolism generating potentially toxic *para*-quinone methide intermediates[55] is not the major cause of tetrandrine-induced hepatotoxicity. Most of the *seco*-analogues **sc1**-**sc5** and racemic muraricine (*rac*-**34**) that do contain the putatively problematic methoxy or hydroxy group at C-12 did not exhibit a notably increased toxicity compared to the RMS compounds, although a direct comparison was not made. This provides further evidence, that the proposed metabolic pathway is not the underlying mechanism for the alkaloid's toxicity.

4.4 MTT ASSAY

For a rapid and rough evaluation of cytotoxicity the (iso)tetrandrine analogues **RMS1**-**RMS10** and the *seco*-analogues **sc1**-**sc5**, as well as the natural products muraricine (*rac*-**34**), berbanine (**35**) and berbidine (**36**) were submitted to a routine MTT assay following the standard protocol of Mosmann[151]. The assay was performed in human leukemia cell line HL-60 and Triton® X-100 was used as positive control.

Table 10. Results of the MTT assay as IC_{50}-values. *The synthetic (racemic) alkaloid was used for testing.

compound	IC_{50} [µM]	compound	IC_{50} [µM]
(iso)tetrandrine analogues		*seco*-analogues	
RMS1	2.6	**sc1**	> 50
RMS2	10.9	**sc2**	30.7
RMS3	7.7	**sc3**	19.5
RMS4	6.5	**sc4**	13.1
RMS5	15.4	**sc5**	17.1
RMS6	>50	natural products	
RMS7	14.6	**tetrandrine** (**1**)	21.2
RMS8	14.6	**berbanine** (**35**)*	>50
RMS9	>50	**berbidine** (**36**)*	>50
RMS10	24.1	**muraricine** (*rac*-**34**)*	>50

As already mentioned the results of this assay only allows an approximate estimation of the acute cytotoxicity of a compound. An IC_{50} value of ≤ 5 µM in the MTT assay can be considered as strongly cytotoxic, substances with a value above 50 µM can be usually expected to be non-toxic. IC_{50} values in between can indicate potential cytotoxic properties to a certain extent.

Since the majority of compounds already exhibited antiproliferative and toxic properties on cancerous cell lines (see chapter **4.1** and **4.3**), toxic effects on human leukemia (HL-60) cells are to be expected as well. The most toxic compounds identified by MTT assay are **RMS1**, **RMS3** and **RMS4**, which are in the range (**RMS3** and **RMS4** very closely) of strong toxicity. In direct comparison to tetrandrine (**1**) (IC_{50} = 21.2 µM), two thirds of all synthesized analogues exhibit lower IC_{50} values than the lead structure. The analogues **RMS6**, **RMS9** and **sc1** as well as the synthetic alkaloids berbanine (**35**), berbidine (**36**) and racemic muraricine (*rac*-**34**) did not show notable cytotoxic effects in this assay (IC_{50} > 50 µM). This data is approximately in line with the observed trend in the assessment of toxicity and antiproliferative activity.

4.5 AGAR DIFFUSION ASSAY

As part of a routine screening most of the synthesized analogues as well as the natural products muraricine (*rac*-**34**), berbanine (**35**) and berbidine (**36**) were tested for antimicrobial activity in a standard agar diffusion assay. Since there is an antimicrobial effect reported for some isoquinoline and benzylisoquinoline alkaloids[152], this sreening was mainly intended for the less complex alkaloids muraricine (*rac*-**34**), berbanine (**35**) and berbidine (**36**) as well as the *seco*-analogues **sc1**-**sc5**. Among the macrocyclic analogues **RMS1**-**RMS10** only the (*R*,*R*/*S*,*S*) isomers (**RMS2**, **RMS4**, **RMS6**, **RMS8**) and **RMS10** were tested. As there was mostly no substantial difference observed between the diastereomers of **RMS1**-**RMS10** regarding biological activity in the other afore mentionend assays, it should be sufficient to test only one isomer as representative of each variation. The compounds were tested against Gram-positive (*Streptococcus entericus*, *Staphylococcus equorum*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas marginalis*), and against fungi (*Yarrowia lipolytica*, *Saccharomyces cerevisiae*). For a positive control tetracycline was used as reference substances for antibacterial and clotrimazole for antifungal activity. There was no zone of inhibition observed in any experiment, consequently none of the substances exhibits antimicrobial activity against the tested germs.

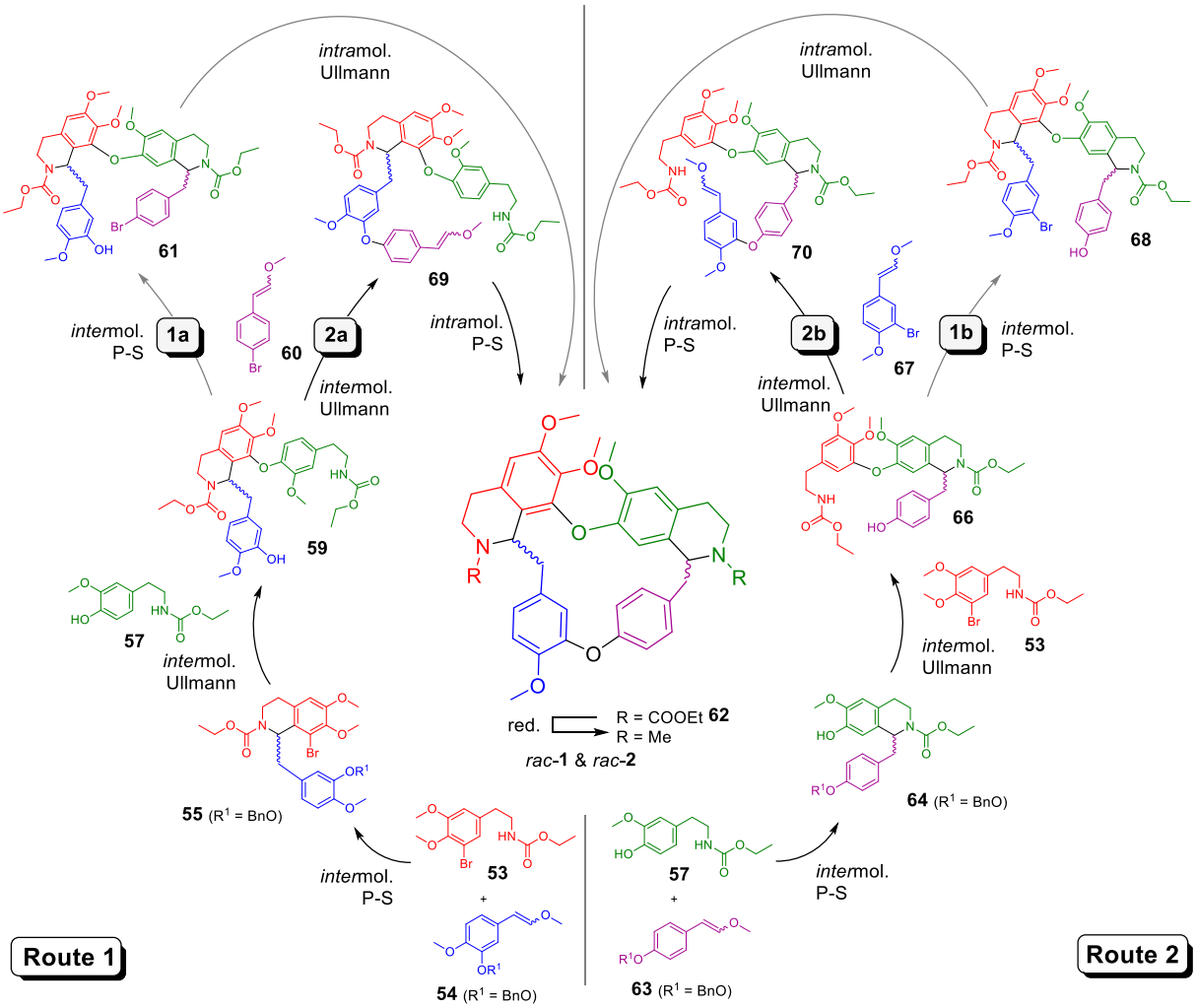
5 SUMMARY

Taken together, five natural products were successfully synthesized in this work. The bisbenzylisoquine alkaloids tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) as well as the isoquinoline-benzylisoquinoline alkaloid muraricine (*rac*-**34**) were synthesized in their racemic form. With the synthetic approaches towards muraricine (*rac*-**34**) and the isoquinolon-isoquinoline alkaloids berbanine (**35**) and berbidine (**36**) the first total syntheses of these alkaloids were developed.

In a first step a suitable method for the construction of the tetrahydroisoquinoline moiety, which is present in four of the five synthesized alkaloids, was investigated. As an *N*-acyl Pictet-Spengler reaction seems most promising and straightforward, this approach was selected as method of choice and different alternatives for aldehydes were tested as suitable building blocks. Beside the efficiency of this reaction step, the good availability and variability of starting material was of interest. For this purporse alkynes, nitrostyrenes (as precursors of *in situ* generated enamines and phenylacetaldehydes) and enol ethers were examined in acid-catalyzed *N*-acyl Pictet-Spengler condensations with an *N*-acylated arylethylamine as model reaction partner. Neither the alkyne nor the nitroalkene could be successfully reacted under various reaction conditions. When using an enol ether as masked aldehyde an efficient cyclization resulting in the desired tetrahydroisoquinoline was accomplished. As this protocol was already applied successfully in our group, the feasibility could be once again confirmed. This method proved to be a straightforward and fast access for the tetrahydroisoquinoline scaffold in the racemic synthesis of tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) with yields from 47% to almost quantitative conversions of 96%, even for highly substituted starting materials. In contrast to Bischler-Napieralski protocols, which require three sequential steps, the construction of the tetrahydroisoquinoline moiety was accomplished in only one step *via* *N*-acyl Pictet-Spengler reaction. The required enol ethers of their part are accessed in a single operation from corresponding benzaldehydes *via* Wittig olefination in high yields. Moreover, the acylated phenenthylamines required for this approach are as well accessible from aromatic aldehydes *via* Henry reaction, subsequent reduction and acylation. In consequence, all four aromatic rings in the target molecule derive from benzyaldehydes, providing a high synthetic flexibility, as a great variety of benzaldehydes is commercially available.

The primary goal of this thesis was to design a new synthetic approach to the bisbenzylisoquine alkaloids tetrandrine (**1**) and isotetrandrine (**2**), which is - compared to the already published syntheses - shorter in the sequence of required steps and superior in terms of yields. From views of a diversity oriented synthetic approach, the development of a flexible protocol that allows to implement systematic structure variations on the aromatic rings for

subsequent structure-activity relationship studies, was also aimed for. Any aromatic ring, which is subject of structure variations can be inserted in a late stage of the synthesis, starting with aromatic aldehydes as building blocks. For this purpose the routes 1a and 1b were developed, in which either the one or the other benzylisoquinoline unit, each representing one half of the target molecule, is synthesized first. Although the synthesis was designed as a primarily racemic approach, the achievement of diastereoselectivity to a certain extent *via* asymmetric induction was gained in an *intra*molecular Pictet-Spengler cyclization step. In addition to the main routes 1a and 1b, in which the cyclization takes place in an *intra*molecular Ullmann-type coupling reaction, the variations 2a and 2b were created. Herein the macrocycle is constructed *via* an *intra*molecular *N*-acyl Pictet-Spengler reaction under formation of the second asymmetric centre. Scheme **31** gives a concise overview of the total synthesis *via* the four different routes.



Scheme 31. Racemic synthesis of the bisbenzylisoquinoline alkaloids tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) on four different routes. Conditions for a) *inter*molecular *N*-acyl Pictet-Spengler reaction (*inter*mol. P-S): TFA, DCM, 0 °C to rt. b) *Intra*molecular *N*-acyl Pictet-Spengler reaction (*intra*mol. P-S): TFA, DCM, -15 °C. c) *Inter*molecular and *intra*molecular Ullmann-type cross-coupling reaction (*inter*mol./*intra*mol. Ullmann): CuBr·Me_2S, Cs_2CO_3, pyridine, 110 °C. d) Carbamate reduction (red.): $LiAlH_4$, THF, 50 °C.

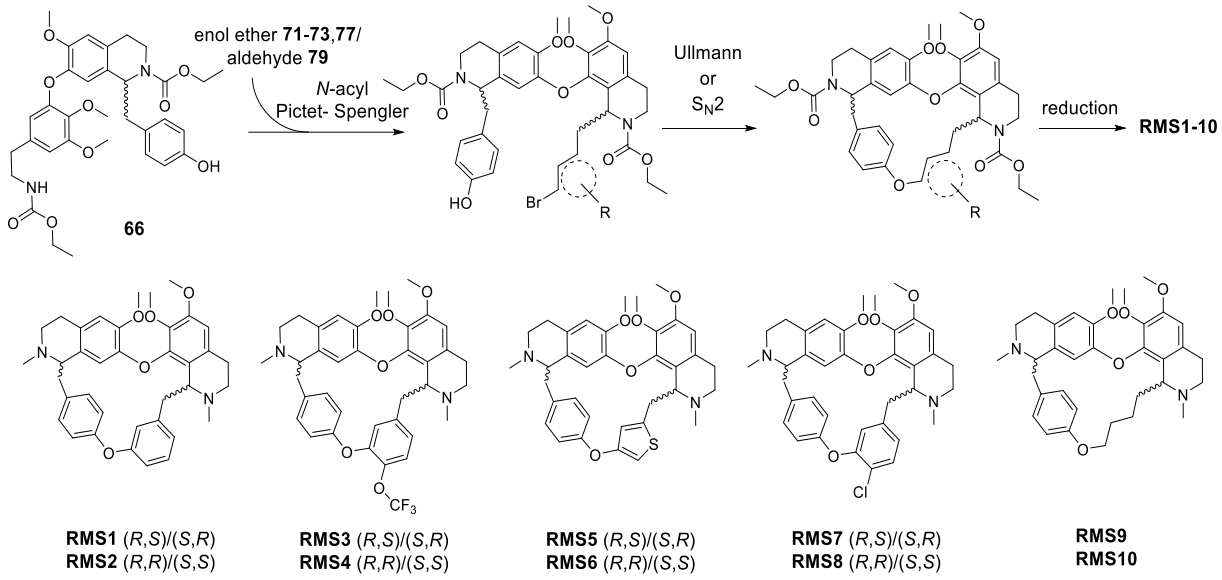
The total synthesis of racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) was achieved in 12 steps each, starting from commercially available buildings blocks on four different routes. Compared to the published syntheses a significant reduction of steps was achieved as Inubushi's approach implies more than 20 steps and the one published in a Chinese patent, 19 steps. The aim of an improved synthetic approach was also reached in terms of efficiency when comparing the overall yields of both approaches. The overall yields (as sum of both alkaloids *rac*-**1** and *rac*-**2**) when combining the building blocks **53**, **54**, **57** and **60** in routes 1a and 2a (or building blocks **53**, **57**, **63** and **67** in routes 1b and 2b respectively) amounts 10.5% in route 1a and 3.0% in route 2a, 12.4% in route 1b and 19.2% in route 2b. As in Inubushi's approach the overall yield amounts 2.1% after combination of corresponding building blocks the herein presented synthetic method is up to nine times more efficient. The greatest enhancement of yields was achieved in the formation of the tetrahydroisoquinoline moiety. Following the *N*-acyl Pictet-Spengler approach this scaffold was constructed in one single operation in yields of 47 – 96%, whereas in Inubushi's synthesis the tetrahydroisoquinoline units were generated in yields from 28 – 35% over three steps *via* Bischler-Napieralski reaction. Consequently, a significant reduction of required steps could be achieved in this new approach.

For the construction of the diaryl ether moiety various conditions following Buchwald-Hartwig and copper-mediated Ullmann-type protocols using different ligand/catalyst systems were explored. The most efficient method by far was the combination of $CuBr \cdot Me_2S$ as catalyst without an additional ligand and Cs_2CO_3 as base in pyridine, a protocol that was previously applied by Evano and coworkers for the synthesis of a macrocyclic phenethyltetrahydroisoquinoline alkaloid[125]. With this method also the yields of diaryl ethers could be partly improved, which were afforded in yields of 41 – 64%, compared to 42 – 48% yield (according to the experimental section[96]) in Inubushi's approach.

Through the routes 2a and 2b in which the macrocyclic (iso)tetrandrine precursor **62** is generated *via* an *intra*molecular *N*-acyl Pictet-Spengler cyclization, diastereoselectivity could be achieved to a certain degree. Favouring the relative stereoconfiguration of tetrandrine (**1**) in route 2a preferably (*R*,*R*)/(*S*,*S*) isomers were formed in a diasteremeric ratio of 87:13, whereas in route 2b predominantly isotetrandrine-type (*S,R*)/(*R,S*) isomers were obtained in a diasteremeric ratio of 71:29. Inubushi obtained prefereably tetrandrine-type isomers in the reduction step of a macrocyclic 3,4-dihydroisoquinoline intermediate to the corresponding tetrahydroisoquinoline with a d.r. of 4:1.

With an efficient synthetic protocol in hand, the synthesis of novel bisbenzylisoquinolines of the (iso)tetrandrine-type were realized. Following route 1b and using the intermediate **66** of the tetrandrine synthesis as starting material, five structure variations could be synthesized as analogues of racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**) respectively. Hereby the

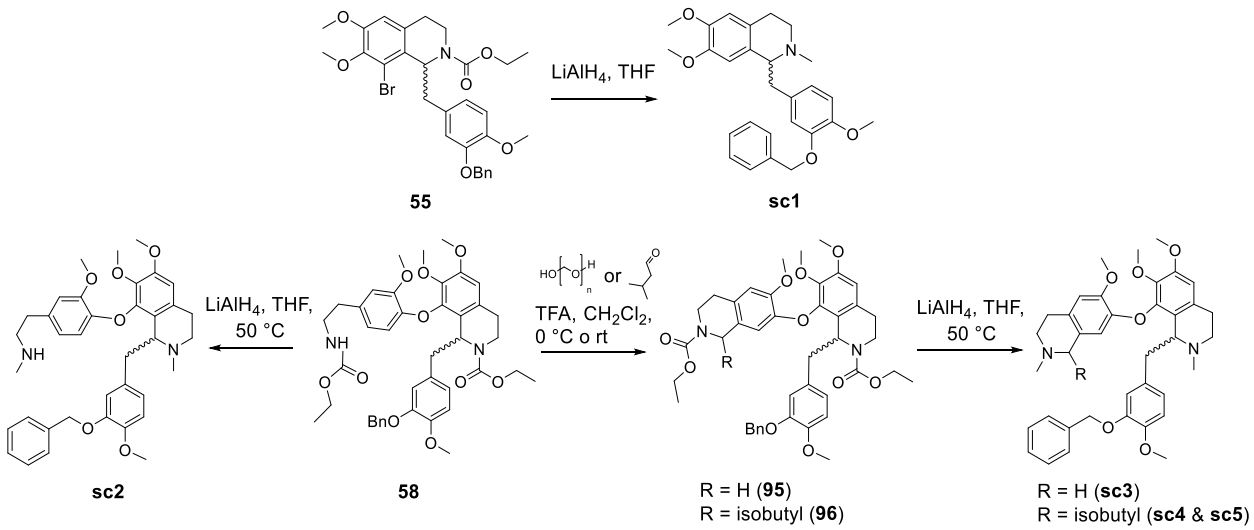
variation focused on the methoxy group at C-12 in ring C, which is discussed for being responsible for the alkaloid's toxicity by being transformed to a quinone methide intermediate in an oxidative metabolism pathway. The methoxy group was successfully eliminated resulting in variations **RMS1** and **RMS2** or replaced by metabolically stable trifluoromethoxy (**RMS3** and **RMS4**) or chlorine substituents (**RMS7** and **RMS8**). In **RMS5** and **RMS6** the complete benzene ring C was replaced by a thiophene ring and in **RMS9** and **RMS10** the aromatic system was completely exchanged for an alkyl chain. In Scheme **32** the synthetic approach to the analogues **RMS1**-**RMS10** is summarized.



Scheme 32. Synthesis of macrocyclic (iso)tetrandrine analogues **RMS1**-**RMS10**. Conditions for a) *N*-acyl Pictet-Spengler reaction: TfOH, DCM, 0 °C to rt. b) Ullmann-type cross-coupling reaction (for the intermediates of variants **RMS1**-**RMS8**): $CuBr{\cdot}Me_2S$, Cs_2CO_3, pyridine, 110 °C. c) S_N2 reaction (for the intermediates of variants **RMS9**/**RMS10**): KI, K_3PO_4, DMF, 100 °C. d) Carbamate reduction (for **RMS1**-**RMS6**, **RMS9**/**RMS10**): $LiAlH_4$, THF, 50 °C. e) Cleavage of carbamates and subsequent reductive *N*-methylation (compounds **RMS7**/**RMS8**): 1) MeLi, THF, 0 °C, 2) aq. formaldehyde solution (37%), $NaBH_3CN$, MeOH, rt.

The syntheses were conducted following the standard protocols established in the synthesis of (iso)tetrandrine except for the variations **RMS7**/**RMS8** and **RMS9**/**RMS10**. For **RMS7**/**RMS8**, in which a chlorine substituent is present, an alternative method for the conversion of the carbamate to *N*-methyl groups was required, as the use of $LiAlH_4$ led to substantial dechlorination. Cleavage of the carbamate groups using MeLi and subsequent reductive *N*-methylation of the resulting secondary amines furnished the desired *N*-methylated bisbenzylisoquinolines **RMS7** and **RMS8**. For the construction of the aliphatic ether bridge in variants **RMS9**/**RMS10** an S_N2 reaction was applied instead of the standard copper-catalyzed protocol for Ullmann cross-coupling. The relative stereoconfigurations of **RMS1**-**RMS8** could be determined by NMR according to a method of Guinaudeau *et al.*[140]. The stereochemistry of the variants **RMS9**-**RMS10** unfortunately remains obscure, since an analysis *via* NMR or X-ray christallography due to unsuccessful christallization failed.

For the synthesis of the *seco*-analogues **sc2**-**sc5** intermediate **58** of the tetrandrine synthesis served as starting material. The *O*-benzyl residue of **58** mimicks the second diaryl ether bridge present in the parental molecule. The reduction of **58** following the standard reduction protocol gave compound **sc2**. The condensation of **58** *via* standard *N*-acyl Pictet-Spengler condensation with either paraformaldehyde or isovaleraldehyde and subsequent reduction gave **sc3**-**sc5** (Scheme **33**). As a second asymmetric centre is built in the reaction of intermediate **58** with isovaleraldehyde, two diastereomers are generated in this reaction consequently. Although the separation of the two diastereomeric intermediates *via* FCC was possible, the determination of the relative stereoconfiguration of **sc4** and **sc5** by NMR or christallographic methods could not be achieved.



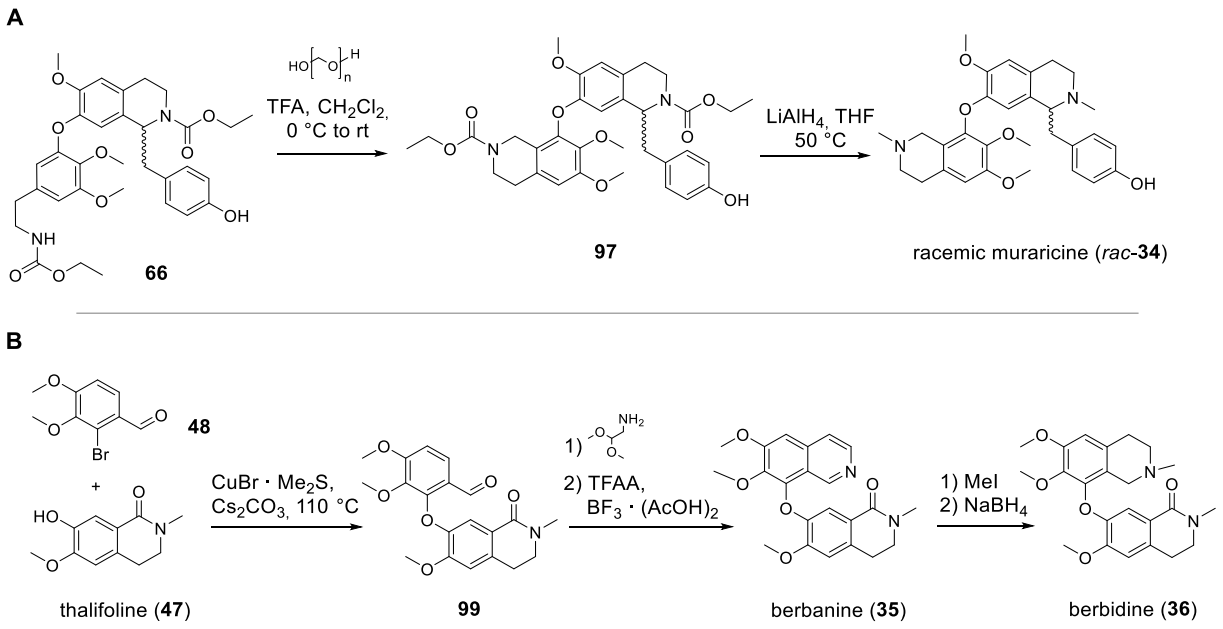
Scheme 33. Synthesis of *seco*-analogues **sc1**-**sc5**.

The monomeric benzylisoquinoline **sc1** was obtained from intermediate **55** in one step by lithium alanate reduction (Scheme **33**).

As an additional synthetic challenge, the related alkaloids berbanine (**35**), berbidine (**36**) and muraricine (**34**) (in its racemic form) were synthesized. Racemic muraricine (*rac*-**34**) was obtained in two steps from **66** (an intermediate of the tetrandrine synthesis) *via* *N*-acyl Pictet-Spengler condensation with paraformaldehyde and subsequent reduction following standard protocols (Scheme **34**, **A**). This represents the first total synthesis of racemic muraricine (*rac*-**34**) in a total of 10 steps from commercially available building blocks in an overall yield of 3.8% along the longest sequence.

The isoquinolone-isoquinoline alkaloids berbanine (**35**) and berbidine (**36**) (Scheme **34**, **B**) were synthesized in one sequence starting with thalifoline (**47**) and 2-bromo-3,4-dimethoxybenzaldehyde (**48**), which were reacted in an Ullmann cross-coupling applying the established protocol for diaryl ether synthesis. In a Pomeranz-Fritsch reaction diaryl ether **99** was converted into the isoquinoline alkaloid berbanine (**35**), which was then *N*-methylated at

the pyridine ring and reduced to berbidine (**36**). The overall yields amount 18% for berbanine (**35**) and 16% for berbidine (**36**) along the longest sequence of steps. With this synthetic protocol, the first total synthesis of both alkaloids was developed.



Scheme 34. First total syntheses of (**A**) racemic muraricine (*rac*-**34**) and (**B**) berbanine (**35**) and berbidine (**36**).

The successful syntheses of the alkaloids berbanine (**35**), berbidine (**36**) and racemic muraricine (*rac*-**34**) demonstrated the general applicability and robustness of these protocols for the diaryl ether synthesis and the *N*-acyl Pictet-Spengler reaction. Both reaction types were previously established for the synthesis of racemic tetrandrine (*rac*-**1**) and isotetrandrine (*rac*-**2**).

As anticancer effects and multidrug resistance reversing activities are well documented for several (bis)benzylisoquinoline alkaloids, among them tetrandrine (**1**)[39, 41, 52, 153] and isotetrandrine (**2**)[12], the successfully synthesized macrocyclic analogues **RMS1**-**RMS10**, the *seco*-analogues **sc1**-**sc5** and racemic muraricine (*rac*-**34**) were submitted to a screening for antiproliferative and P-gp inhibitory activity. The compounds were also evaluated with regard to their toxic potency through extensive *in vitro* toxicity assessment, as undesired cytotoxic side effects are described for several bisbenzylisoquinoline alkaloids including tetrandrine (**1**)[54]. Although the analogues **RMS1**-**RMS10** that were specifically designed for the reduction of tetrandrine's (**1**) toxicity by replacement or amendment of the putatively metabolic instable methoxy group at C-12, these variants were not found to possess a considerably improved toxicity profile in several cellular models. In contrast, several analogues exhibited even increased toxic effects. The hypothesized CYP-mediated metabolic pathway was therefore not found to be the major cause of tetrandrine-induced toxicity and the underlying molecular

mechanism remains to be elucidated. Consequently, a different strategy for the reduction of the alkaloid's toxicity needs to be investigated.

Whereas the chemoresistance reversing activity by the inhibition of the efflux pump P-gp was largely equal to the lead structure tetrandrine (**1**) in the majority of compounds, several analogues exhibited markedly increased antiproliferative potency, especially among the series of macrocyclic analogues. Taking the results of pharmacological characterization and the toxicity assessment together, **RMS3** and **RMS5** emerged as promising compounds, as they showed strongly enhanced antiproliferative activity, possess chemoresistance reversing properties in low doses and do not display an unfavourable toxicity profile compared to tetrandrine (**1**). Due to their higher potency, a reduction of required dose might in turn lead to diminished side effects when applying the substances *in vivo*.
Also among the *seco*-analogues **sc1**-**sc5** compounds with antitumoral properties could be identified. Especially **sc4** and **sc5** showed increased antiproliferative activity and significant multidrug resistance reversing properties, albeit toxic effects similar or - depending on the used *in vitro* model - stronger compared to that of tetrandrine (**1**) were observed.

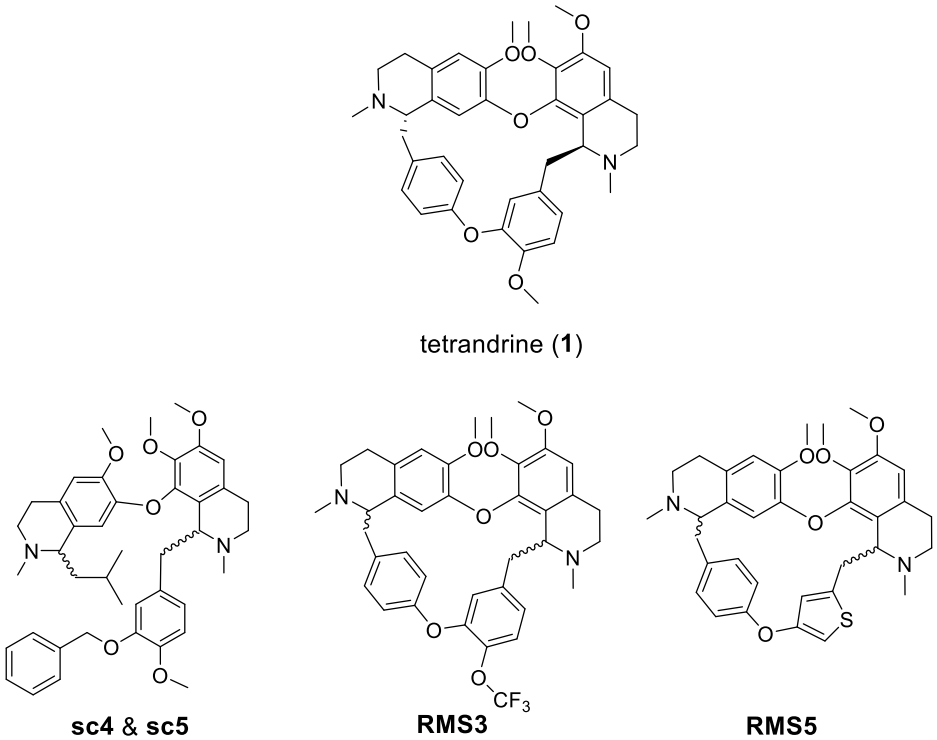


Figure 21. Most promising analogues of (iso)tetrandrine with antitumoral activity synthesized in this work.

The natural product muraricine in its racemic form (*rac*-**34**) could be identified as a moderate but non-toxic inhibitor of P-gp. These results show that not only complex bisbenzylisoquinolines but also simplified analogues are capable of relevant pharmacological activity.

As the number of structure variations synthesized in this project is comparably small, further systematic structure variations for the investigation of structure-activity relationships are required. The modular and effective synthetic approach to the bisbenzylisoquinolines of the tetrandrine-type developed in this thesis should pave the way for the access of diverse structure variations with modifications at nearly all positions. Consequently, this work enables to significantly extend the chemical diversity of libraries of bisbenzylisoquinolines, a class of pharmacologically interesting alkaloids that is far away from being exploited. Early pharmacological evaluation of exemplarly synthesized variations provided encouraging data as a good starting point for future medicinal chemistry projects.

6 EXPERIMENTIAL SECTION

6.1 GENERAL SPECIFICATIONS AND PARAMETERS

6.1.1 INSTRUMENTS

Nuclear magnetic resonance spectroscopy

NMR spectra were recorded with a 400 MHz (400 MHz for ^{1}H and 101 MHz for ^{13}C), 500 MHz (500 MHz for ^{1}H and 126 MHz for ^{13}C), 600 MHz (599 MHz for ^{1}H and 151 MHz for ^{13}C) or 800 MHz (800 MHz for ^{1}H and 201 MHz for ^{13}C) Avance III HD Bruker Biospin spectrometer (Bruker, USA). Peak assignments were based on 2D NMR experiments using standard pulse programs (COSY, HSQC/HMQC, DEPT, HMBC and if required NOESY). Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.0 ppm). For the characterization of rotamers a temperature program was employed for recording both 1D and 2D spectra. Hereby chemical shifts were referenced to the signal of tetramethylsilane in deuterated tetrachloroethane (Tcl_2 [100 °C]: δ_H = 5.92 ppm, δ_C = 74.0 ppm). The spin multiplicity is expressed as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations thereof.

Mass spectrometry

High resolution mass spectra (HR-MS) were recorded using a Thermo Finnigan MAT 95 or Thermo Q Exactive GC Orbitrap (Thermo Fisher Scientific, USA) instrument for electron impact ionisation (EI). Thermo Finnigan LTQ FT (Thermo Fisher Scientific, USA) was used for electrospray ionisation (ESI).

For reaction monitoring low resolution mass spectra were recorded on an expression^{L} CMS device (Advion, USA) by atmospheric pressure solids analysis probe (ASAP) and atmospheric-pressure chemical ionization (APCI) for the analysis of samples in solution or neat solids. For the analysis of spots on a TLC plate, the measurement was carried out in combination with a Plate Express® TLC Plate Reader device (Advion, USA) using APCI or ESI ionization method. Additionally, reaction monitoring was performed *via* GC-MS using a Hewlett Packard 5989A instrument (Hewlett Packard, USA).

Infrared spectroscopy

IR spectra were recorded using a Jasco FT/IR-4100 (type A) instrument (Jasco, Germany) equipped with a diamond ATR unit (Jasco PRO450-S).

Melting points

Melting points were determined by open capillary method on a Büchi B-540 apparatus (Büchi). All values are given in °C and are uncorrected.

High pressure liquid chromatography

For quantitative analysis and for the determination of purity HPLC was performed on a HP Agilent 1100 system (Agilent Technologies, Germany) equipped with an Agilent G1315A 1100/1200 diode array detector, a G1311A QuatPump pump system and a G1316A ColComp column oven. Following columns and parameters were used for separation:

Agilent InfinityLab Poroshell 120 EC-C18 (2.7 µm, 100 x 3.0 mm) (1)
Agilent Zorbax Eclipse Plus C18 (5.0 µm, 150 x 4.6 mm) (2)

Table 11. Parameters for analytical HPLC.

method	column	eluent	flowrate [mL/min]	temp. [°C]
a	1	50% ACN, 49.9% water, 0.1% THF	0.8	50
b	2	70% ACN, 30% water	0.8	50
c	2	80% MeOH, 20% water, NaOH-buffer pH 9	0.8	50
d	2	70% ACN, 30% water, formic acid	1.0	35
e	2	50% ACN, 50% water	0.8	50

The diastereomeric ratios of compounds **61**, **62**, **68** and **97** were determined using method a.

Preparative HPLC was performed on a VWR LaPrep P110 system (VWR, USA) equipped with a UV Detector P311 using a Nucleodur® 100-5 column (5.0 µm, 250 x 10.0 mm; Macherey-Nagel, Germany).

Microwave assisted synthesis

Microwave assisted synthesis was carried out in a Discover (S-Class Plus) SP (CEM, USA) microwave reactor.

6.1.2 BIOLOGICAL ASSAYS

Agar diffusion assay

The bacteria and fungi, purchased from DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Germany), were cultivated on an AC agar (Sigma-Aldrich, Germany) in a cell density of 10^8 bacteria cells per mL and 5 x 10^6 fungi cells per mL. Six-millimeter paper discs (Macherey-Nagel, Germany), impregnated with 30 µg of the tested compound or reference drug (tetracyclin/clotrimazol; both as a 1% [m/V] stock solution in DMSO) were placed on the agar. One disc served as control, which was impregnated with 3.0 µL of DMSO. The bacteria media were incubated for 24 hr at 32 °C, the fungi media for 48 hr at 28 °C under sterile conditions and the diameter of the zone of inhibition (mm) was evaluated. The diameter of the zones of inhibition was manually measured.

MTT assay

The MTT assay was performed using human leukemia cell line HL-60 purchased from DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Germany). The cells were seeded on a 96-well plate (99 µL cell suspension per well) in a cell density of 9 x 10^5 cells per mL and incubated for 24 h at 37 °C.

The compounds were tested in increasing concentrations ranging from 1.25 to 400 µM dissolved in DMSO. The positive control was performed using Triton® X-100 in a concentration of 1 µg/mL, the zero value was determined with DMSO (1 µL per well). 1 µL of each test solution, Triton® X-100 solution or DMSO was added to one well and the cells were incubated for 24 h at 37 °C and 5% CO_2. Subsequently, 10 µL of a MTT-solution (5 mg MTT in 1 mL of phosphate buffered saline (PBS) pH 7.4) were added per well and the culture was incubated for another 2 h under the same conditions. To each well 190 µL of DMSO was then added and the plate left for 1 h. Photometric quantification was performed on an ELISA MRX II Microplate reader (Dynex, Germany) at a wavelength of λ = 570 nm. The statistical analysis and the calculation of the corresponding IC_{50} values was done using Prism 5.0 software (GraphPad, USA).

Calcein retention assay, Nicoletti assay and toxicity assays

These assays were performed by Martin Müller and Franz Geisslinger from the group of Prof. Dr. Angelika Vollmar (chair of pharmaceutical biology, LMU Munich). For the detailed protocols see references no. 53, 122 and 147.

6.1.3 MATERIALS

Chemicals and solvents

All chemicals and anhydrous solvents (septum sealed & stored on molecular sieves) were purchased from Sigma Aldrich (Germany), abcr GmbH (Germany), VWR (Germany), Acros (Belgium), Alfa Aesar/Thermo Fisher Scientific GmbH (Germany), Th. Geyer GmbH & Co. KG (Germany) or TCI Deutschland GmbH. Solvents used for analytical and preparative HPLC were HPLC grade, all solvents used for FCC or any other purpose were p.a. grade (if required) or purified by destillation.

Thin layer chromatography (TLC)

TLC was carried out on polyester plates coated with 0.2 mm silica gel and a fluorescence indicator (POLYGRAM SIL G/UV_{254}, Macherey-Nagel, Germany). For preparative TLC 1 mm PLC silica gel 60 F_{254} plates (20 x 20 cm) with a concentrating zone (Merck, Germany) were used. Visualization was enabled by UV-light using wavelength λ = 254 nm or 365 nm or a suitable dye (Dragendorff reagent, Ehrlich reagent, ceric ammonium sulfate (CAM)-stain, Dinitrophenylhydrazine (DNPH)-stain).

Flash column chromatography (FCC)

Flash chromatography was performed using silica gel 60 (0.040 - 0.063 mm, 230-400 mesh ASTM, Merck, Germany) and the solvent systems indicated in the compound characterization section.

Software

ChemDraw Professional® 16.0 (PerkinElmer, USA) was used for drawing structures or reaction schemes. MestReNova® 10.0 (Mestrelab Research, Spain) was used for processing and analysis of NMR spectra. Chromeleon® 7.2.9. (Thermo Fisher Scientific Dionex, USA) was used for processing and analysis of HPLC spectra. GraphPad Prism® 5.0 and 8.4.3 (GraphPad Software Inc., USA) was used for data visualization and statistical analysis.

6.2 GENERAL PROCEDURES

General procedure 1 - Wittig olefination

A suspension of (methoxymethyl)triphenylphosphonium chloride (1.2 eq.) in anhydrous THF (2 mL per mmol aromatic aldehyde) was cooled to 0 °C under nitrogen atmosphere. A solution of lithium diisopropylamide (1.4 eq., 2.0 M solution in THF) was added dropwise and the resulting mixture stirred for 45 min. A solution of the aromatic aldehyde (1.0 eq.) in anhydrous THF (2 mL per mmol) was added while stirring. The mixture was allowed to warm up to ambient temperature and was stirred for 4 h. The reaction was then quenched with deionized water and extracted 3x with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography.

General procedure 2 - *N*-acyl Pictet-Spengler condensation

A solution of carbamate (1.0 eq.) and enol ether (1.2 – 2.0 eq.) in dichloromethane (for *inter*molecular reactions 10 mL per mmol carbamate) was cooled to 0 °C under nitrogen atmosphere. Trifluoroacetic acid (10 eq.) or trifluoromethanesulfonic acid (TfOH, 0.1 eq., 0.113 mol/L in acetonitrile) was added dropwise. The reaction mixture was allowed to warm up to ambient temperature and was stirred for 6 - 12 h. The *intra*molecular reactions were conducted at a carbamate concentration of 0.01 mM and cooled to -15 °C. After adding TFA (10 eq.) the temperature was kept at -15 °C until the reaction was completed (typically after 12 h; TLC control). A saturated $NaHCO_3$ solution was then added for neutralization and the aqueous phase extracted 3x with dichloromethane. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography.

General procedure 3 - Ullmann-type C–O coupling reaction

According to a modified procedure of Wang *et al*.[125], bromoarene (1.0 – 1.2 eq.), phenol (1.0 – 2.0 eq.), $CuBr{\cdot}Me_2S$ (1.0 eq.) and Cs_2CO_3 (3.0 eq.) were placed in a pressure tube or a flask closed with a screwcap with septum inlet and sealed with PTFE tape. Anhydrous pyridine (for *inter*molecular C–O coupling reactions 10 mL per mmol bromoarene, for *intra*molecular reaction a concentration of 0.02 mM was chosen) was added and after 5 min of pre-stirring the reaction was heated to 110 °C for 2 – 7 days under nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate and filtered over a small plug of silica gel

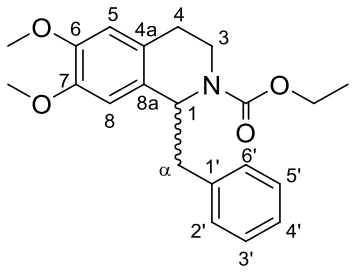
in order to remove the catalyst and the excess base, followed by washing with ethyl acetate. The filtrate was concentrated *in vacuo* to afford a brown oil as crude product, which was purified by column chromatography.

General procedure 4 - carbamate reduction

Lithium alanate (10 eq.) was suspended in anhydrous THF (1.0 mL per 0.02 mmol carbamate) under nitrogen atmosphere. A solution of carbamate (1.0 eq.) in anhydrous THF was added dropwise and the resulting mixture was heated at 50 °C for 4 – 12 h. The reaction was cooled to 0 °C and slowly quenched with water. After alkalizing to pH 12 – 14 with a 2.0 M sodium hydroxide solution, the aqueous phase was then extracted 3x with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product, which was purified by column chromatography.

6.3 CHARACTERIZATION OF COMPOUNDS

N-Ethoxycarbonyl-6,7-dimethoxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline (41)



$C_{21}H_{25}NO_4$

M_W = 355.18 g/mol

Carbamate **39** (500 mg, 1.97 mmol) and enol ether **46** (530 mg, 3.95 mmol) were condensed following General Procedure 2 (for *inter*molecular *N*-acyl Pictet-Spengler reaction) to give tetrahydroisoquinoline **41**. The reaction was completed after 2 h. The crude product was purified by flash column chromatography (dichloromethane, R_f = 0.12) and the title compound obtained as a white solid.

yield: 489 mg, 1.40 mmol, 71%, white solid

mp: 116.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.26 – 7.20 (m, 2H, 5'-H, 3'-H), 7.20 – 7.15 (m, 1H, 4'-H), 7.10 – 7.05 (m, 2H, 6'-H, 2'-H), 6.58 (s, 1H, 5-H), 6.24 (s, 1H, 8-H), 5.19 (t, *J*=6.9, 1H, 1), 4.09 – 3.93 (m, 3H, 3-H, OC*H*$_2$CH$_3$), 3.79 (s, 3H, 6-OCH$_3$), 3.60 (s, 3H, 7-OCH$_3$), 3.31 (ddd, *J*=13.6, 9.5, 4.6, 1H, 3-H), 3.11 (dd, *J*=13.4, 6.6, 1H, α-H), 2.95 (dd, *J*=13.3, 7.0, 1H, α-H), 2.79 (ddd, *J*=15.6, 9.5, 5.9, 1H, 4-H), 2.58 (dt, *J*=15.9, 4.5, 1H, 4-H), 1.17 (t, *J*=7.1, 3H, OCH$_2$C*H*$_3$)

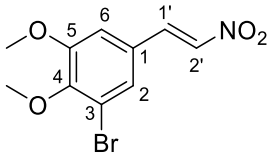
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (C=O), 148.6 (C-6), 147.8 (C-7), 138.6 (C-1'), 129.8 (C-6', C-2'), 129.1 (C-8a), 128.2 (C-5', C-3'), 126.8 (C-4a), 126.4 (C-4'), 113.1 (C-5), 112.2 (C-8), 61.2 (O*C*H$_2$CH$_3$), 56.4, 56.3, 56.3 (7-OCH$_3$, 6-OCH$_3$ and C-1) 43.1 (C-α), 38.8 (C-3), 28.1 (C-4), 14.6 (OCH$_2$*C*H$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2918, 1677, 1519, 1465, 1434, 1229, 1208, 1100, 858, 762, 698

Purity (HPLC, method d) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{21}H_{25}NO_4 + H]^+$ 356.1856, found: 356.1859

(*E*)-3-Bromo-4,5-dimethoxy-1-(2-nitrovinyl)benzene (51)



$C_{10}H_{10}BrNO_4$

M_W = 286.98 g/mol

Synthesized according to a procedure of Maresh *et al*.[122]:

To a mixture of 3-bromo-4,5-dimethoxybenzaldehyde (**50**, 10.5 g, 42.8 mmol) and ammonium acetate (3.30 g, 42.8 mmol, freshly recrystallized from glacial acetic acid) a small number of 3Å molecular sieves were added as well as glacial acetic acid (35 mL) and nitromethane (11.5 mL, 214 mmol) under nitrogen atmosphere. After heating the reaction at 95°C for 16 h, the molecular sieves were removed and the resulting dark solution was quenched with 100 mL of brine. The aqueous phase was extracted with ethyl acetate (3x 500 mL), the combined organic phases washed with deionized water (3x 500 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow crystalline solid. The crude product can be recrystallized from methanol as well as purified by flash column chromatography (50% dichloromethane in hexanes, R_f = 0.25). For recrystallization the nitrostyrene was dissolved in a minimal amount of methanol at 50°C. After cooling to 0 °C the solid was vacuum filtered over Buchner funnel and washed with few chilled methanol (0 °C) until the crystals appear bright yellow.

yield: 7.37 g, 25.7 mmol, 60 %, bright yellow crystalline solid

mp: 153.5 °C (lit.[122]: 150.0 – 153.2 °C)

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.88 (d, J = 13.6 Hz, 1H, 1'-H), 7.51 (d, J = 13.6 Hz, 1H, 2'-H), 7.37 (d, J = 2.1 Hz, 1H, 2-H), 6.98 (d, J = 2.0 Hz, 1H, 6-H), 3.92 (s, 3H, 4-OCH_3), 3.92 (s, 3H, 5-OCH_3)

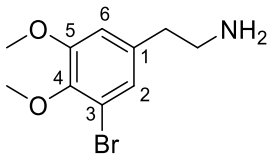
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 154.2 (C-5), 149.9 (C-4), 137.7 (C-1'), 137.3 (C-2'), 127.0 (C-1), 126.4 (C-2), 118.7 (C-3), 111.6 (C-6), 61.0 (4-OCH_3), 56.4 (5-OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2919, 1628, 1414, 1352, 1279, 1151, 1044, 962, 831

Purity (HPLC, method a) = 92% (λ = 210 nm)

HRMS (EI): *m/z* calcd for $[C_{10}H_{10}{}^{79}BrNO_4]^{\bullet+}$ 286.9788, found: 286.9801

3-Bromo-4,5-dimethoxy-phenethylamine (52)



$C_{10}H_{14}BrNO_2$

M_W = 259.02 g/mol

Synthesized according to a procedure of Maresh *et al.*[122]:

In an open round bottom flask 50 mL of methanol were cooled to 0 °C. Over a period of 60 min. the nitrostyrene **51** (7.37 g, 25.7 mmol), 37% HCl (48.2 mL, 514 mmol) and zinc (16.8 g, 257 mmol) were added alternately, each in small portions while vigorously stirring and maintaining the temperature at 0° C. The reaction was allowed to stir for 12 h at 0 °C. The disappearance of the yellow colour indicates complete reduction, which was confirmed by TLC analysis (R_f = 0.26, 10% methanol in dichloromethane). The excess solid zinc was removed by filtration through filter paper. To the filtrate 160 mL of saturated methanolic sodium hydroxide solution were added to alkalize the solution to pH 12, which results in a white precipitation. After adding 260 mL chloroform, the mixture was vacuum filtered over a Buchner funnel. The remaining paste was extracted with chloroform (3x 250 mL) and filtered under vacuum. To avoid compound decomposition the temperature was kept below 5 °C during all extraction and filtration steps. The combined organic phases were dried over $MgSO_4$, filtrated and concentrated *in vacuo* to afford an orange oil (6.59 g). The crude product was used in the following step without purification.

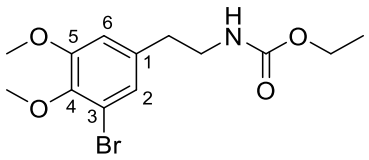
^{1}H NMR (500 MHz, MeOD) δ [ppm] = 7.06 (d, J = 2.0 Hz, 1H, 2-H), 6.94 (d, J = 1.9 Hz, 1H, 6-H), 3.88 (s, 3H, 5-OCH_3), 3.78 (s, 3H, 4-OCH_3), 3.09 (t, J = 8.1, 6.8 Hz, 2H, NCH_2-CH_2), 2.86 (t, 2H, NCH_2-CH_2)

^{13}C NMR (126 MHz, MeOD) δ [ppm] = 155.3 (C-5), 146.6 (C-4), 136.5 (C-1), 125.7 (C-2), 118.4 (C-3), 113.8 (C-6), 60.8 (4-OCH_3), 56.6 (5-OCH_3), 42.6 (NCH_2-CH_2), 35.6 (NCH_2-CH_2)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3326, 1645, 1488, 1415, 1279, 1238, 1140, 1040, 999

HRMS (ESI): *m/z* calcd for $[C_{10}H_{14}{}^{79}BrNO_2 + H]^+$ 260.0286, found: 260.0282

3-Bromo-*N*-ethoxycarbonyl-4,5-dimethoxyphenethylamin (53)



$C_{13}H_{18}BrNO_4$

M_W = 331.04 g/mol

Phenethylamine **52** (6.48 g, 25.0 mmol) was dissolved in dichloromethane (100 mL) under nitrogen atmosphere and the solution cooled to 0 °C. Triethylamine (14.1 mL, 101 mmol) was added followed by ethyl chloroformate (6.06 mL, 63.4 mmol) in a dropwise fashion. The reaction was allowed to warm to ambient temperature and was stirred for 14 h. TLC analysis showed conversion to a less polar product (R_f = 0.33, 25% ethyl acetate in hexanes). The reaction was then quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with dichloromethane (3x 80 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo* to afford a yellow oil. Purification was accomplished by flash column chromatography (25% ethyl acetate in hexanes, R_f = 0.33).

yield: 5.89 g, 17.5 mmol, 70%, pale yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.96 (d, J = 1.9 Hz, 1H, 2-H), 6.69 – 6.66 (m, 1H, 6-H), 4.68 (s, 1H, NH), 4.11 (q, J = 7.1 Hz, 2H, OCH_2-CH_3), 3.85 (s, 3H, 5-OCH_3), 3.83 (s, 3H, 4-OCH_3), 3.40 (q, J = 6.8 Hz, 2H, NCH_2-CH_2), 2.73 (t, J = 7.0 Hz, 2H, NCH_2-CH_2), 1.23 (t, J = 7.1 Hz, 3H, OCH_2-CH_3)

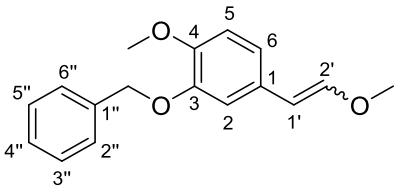
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.7 (C=O), 153.8 (C-5), 145.2 (C-4), 136.2 (C-1), 124.8 (C-2), 117.8 (C-3), 112.4 (C-6), 61.0 (O$C$$H_2$-$CH_3$), 60.7 (4-$OCH_3$), 56.2 (5-$OCH_3$), 42.1 (N$C$$H_2$-$CH_2$), 35.9 ($NCH_2$-$C$$H_2$), 14.8 ($OCH_2$-$C$$H_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3354, 2937, 2826, 1697, 1488, 1271, 1235, 1140, 1044, 1001, 817

Purity (HPLC, method a) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{13}H_{18}{}^{79}BrNO_4 + H]^+$ 332.0497, found: 332.0493

(*E/Z*)-3-(Benzyloxy)-4-methoxy-1-(2-methoxyvinyl)benzene (54)



$C_{17}H_{18}O_3$

M_W = 270.13 g/mol

3-Benzyloxy-4-methoxybenzaldehyde (6.01 g, 24.8 mmol) was reacted following General Procedure 1 (Wittig olefination). The reaction was completed after 4 h. Purification was accomplished by flash column chromatography (10% ethyl acetate in hexanes, R_f = 0.30) and the product obtained as white solid (yield 5.89 g, 21.8 mmol, 88%). The major product is the *E*-isomer (*E,Z*-isomer ratio 1:0.82, estimated by NMR-integrals).

yield: 5.89 g, 21.8 mmol, 88%, white solid

mp: 95.5 – 96.0 °C

NMR data of the major *E*-isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.50 – 7.43 (m, 2H, 6''-H, 2''-H), 7.41 – 7.27 (m, 3H, 5''-H, 4''-H, 3''-H), 6.86 (d, *J* = 13.1 Hz, 1H, 2'-H), 6.84 – 6.76 (m, 3H, 2-H, 5-H, 6-H), 5.72 (d, *J* = 12.9 Hz, 1H, 1'-H), 5.16 (s, 2H, OC*H*$_2$-Ph), 3.87 (s, 3H, 4-OCH_3), 3.65 (s, 3H, 2'-OCH_3)

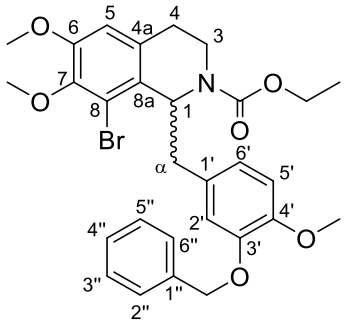
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 148.2 (C-3), 147.9 (C-4), 147.9 (C-2'), 137.4 (C-1''), 129.4 (C-1), 128.7 (C-5'', C-3''), 128.0 (C-4''), 127.5 (C-6'', C-2''), 118.4 (C-6), 112.4 (C-5), 111.4 (C-2), 104.9 (C-1'), 71.3 (O*C*H$_2$-Ph), 56.6 (2'-OCH_3), 56.3 (4-OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3060, 2931, 1638, 1514, 1254, 1134, 1010, 746, 698

Purity (HPLC, method a) = > 99% (λ = 210 nm)

HRMS (EI): *m/z* calcd for $[C_{17}H_{18}O_3]^{\bullet+}$ 270.1251, found: 270.1251

(±)-8-Bromo-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (55)



$C_{29}H_{32}BrNO_6$

M_W = 569.14 g/mol

Carbamate **53** (5.89 g, 17.8 mmol) and enol ether **54** (5.76 g, 21.3 mmol) were condensed following General Procedure 2 (for *inter*molecular *N*-acyl Pictet-Spengler reaction) using TFA as catalyst to give tetrahydroisoquinoline **55**. The reaction was completed after 12 h. The crude product was purified by flash column chromatography (20% acetone in hexanes, R_f = 0.17) and the title compound obtained as a pale yellow solid (4.66 g, 8.19 mmol, 46%).

yield: 4.66 g, 8.19 mmol, 46%, pale yellow solid

mp: 40.5 – 42.5 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) δ [ppm] = 7.46 – 7.41 (m, 2H, 6''-H, 2''-H), 7.38 – 7.32 (m, 2H, 5''-H, 3''-H), 7.31 – 7.26 (m, 1H, 4''-H), 6.79 (d, *J* = 8.1 Hz, 1H, 5'-H), 6.74 (d, *J* = 2.0 Hz, 1H, 2'-H), 6.70 (dd, *J* = 8.1, 2.0 Hz, 1H, 6'-H), 6.60 (s, 1H, 5-H), 5.58 – 5.48 (m, 1H, 1-H), 5.02 (s, 2H, OC*H*$_2$-Ph), 4.03 – 3.84 (m, 3H, H-3, OC*H*$_2$-CH_3), 3.83 (s, 3H, 7-OCH_3), 3.82 (s, 3H, 6-OCH_3), 3.81 (s, 3H, 4'-OCH_3), 3.43 (ddd, *J* = 13.2, 8.8, 5.5 Hz, 1H, 3-H), 3.15 (dd, *J* = 14.3, 3.9 Hz, 1H, α-H), 2.84 – 2.70 (m, 2H, 4-H, α-H), 2.53 (d, *J* = 13.9 Hz, 1H, 4-H), 1.07 (br s, 3H, OCH_2-C*H*$_3$)

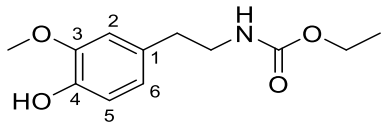
^{13}C NMR (101 MHz, TCl_2, 100 °C) δ [ppm] = 155.5 (*C*=O), 152.3 (C-6), 149.3 (C-4'), 148.8 (C-3'), 145.7 (C-7), 137.9 (C-1''), 131.7 (C-4a), 131.6 (C-1'), 129.9 (C-8a), 128.4 (C-3'', C-5''), 127.7 (C-4''), 127.5 (C-2'', C-6''), 122.9 (C-6'), 118.3 (C-8), 117.5 (C-2'), 113.7 (C-5'), 112.9 (C-5), 72.0 (O*C*H$_2$-Ph), 61.2 (O*C*H$_2$-CH_3), 60.5 (7-OCH_3), 56.8 (4'-OCH_3 or 6-OCH_3), 56.5 (4'-OCH_3 or 6-OCH_3), 56.1 (C-1), 39.1 (C-α), 38.0 (C-3), 28.1 (C-4), 14.5 (OCH_2-*C*H$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2934, 2836, 1691, 1596, 1513, 1425, 1318, 1246, 1137, 1101, 1024, 741, 697

Purity (HPLC, method a) = 98% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{29}H_{32}{}^{79}BrNO_6 + H]^+$ 570.1486, found: 570.1489

***N*-Ethoxycarbonyl-4-hydroxy-3-methoxyphenethylamine (57)**



$C_{12}H_{17}NO_4$

M_W = 239.12 g/mol

3-Methoxytyramine hydrochloride (**56**, 3.46 g, 17.2 mmol) was suspended in dichloromethane (100 mL) under nitrogen atmosphere and the mixture cooled to 0 °C. Triethylamine (9.58 mL, 68.7 mmol) was added, followed by ethyl chloroformate (4.11 mL, 43.0 mmol) in a dropwise fashion. The reaction was allowed to warm to ambient temperature and stirred for 15 h. After this time TLC analysis showed complete conversion to a less polar product (R_f = 0.26, dichloromethane), which is the ethoxycarbonylated phenol intermediate. For chemoselective cleavage of the phenol ester, an ethanolic sodium hydroxide solution (1.0 M, 100 mL) was added to the reaction and the mixture stirred for 2 h at ambient temperature. After addition of hydrochloric acid (2 M, 60 mL) the organic solvents were removed *in vacuo* and the remaining aqueous solution was extracted with dichloromethane (3 x 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a beige oil. Purification by flash column chromatography (30% ethyl acetate in hexanes, R_f = 0.20) gave the title compound as a white solid.

yield: 3.70 g, 15.5 mmol, 90%, white solid

mp: 95.0 – 95.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.84 (d, J = 8.2 Hz, 1H, 5-H), 6.70 – 6.65 (m, 2H, 6-H, 2-H), 5.62 (s, 1H, OH), 4.69 (s, 1H, NH), 4.10 (q, J = 7.1 Hz, 2H, OCH_2-CH_3), 3.86 (s, 3H, OCH_3), 3.39 (q, J = 6.7 Hz, 2H, NCH_2-CH_2), 2.73 (t, J = 7.0 Hz, 2H, NCH_2-CH_2), 1.22 (t, J = 7.1 Hz, 3H, OCH_2-CH_3)

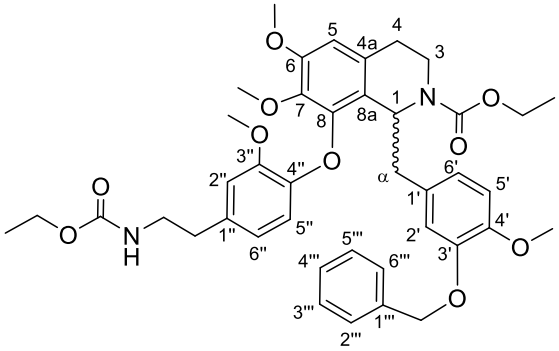
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.8 (C=O), 146.7 (C-3), 144.4 (C-4), 130.7 (C-1), 121.5 (C-2), 114.6 (C-5), 111.4 (C-6), 60.9 (OCH$_2$-CH_3), 56.0 (OCH_3), 42.4 (NCH$_2$-CH_2), 35.9 (NCH_2-CH$_2$), 14.8 (OCH_2-CH$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3368, 3273, 1687, 1518, 1237, 1125, 1033, 824, 781

Purity (HPLC, method a) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{12}H_{17}NO_4 - H]^-$ 238.1085, found: 238.1087

(±)-8-(4-(2-((Ethoxycarbonyl)amino)ethyl)-2-methoxyphenoxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (58)



$C_{41}H_{48}N_2O_{10}$

M_W = 728.33 g/mol

Tetrahydroisoquinoline **55** (3.00 g, 5.26 mmol) and phenol **57** (2.52 g, 10.5 mmol) were coupled following General Procedure 3 (*inter*molecular Ullmann-type C–O coupling reaction). The reaction was completed after 7 days. Purification was accomplished by flash column chromatography (10% ethyl acetate in dichloromethane, R_f = 0.26) and the product obtained as a beige solid.

yield: 1.57 g, 2.16 mmol, 41%, beige solid

mp: 58.5 – 60.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.41 – 7.37 (m, 2H, 6'''-H, 2'''-H), 7.36 – 7.30 (m, 2H, 5'''-H, 3'''-H), 7.30 – 7.25 (m, 1H, 4'''-H), 6.79 (d, *J* = 2.0 Hz, 1H, 2''-H), 6.73 (d, *J* = 8.1 Hz, 1H, 5'-H), 6.66 (d, *J* = 2.0 Hz, 1H, 2'-H), 6.62 – 6.59 (m, 1H, 6'-H), 6.59 – 6.57 (m, 1H, 6''-H), 6.55 (d, *J* = 8.2 Hz, 1H, 5''-H), 6.50 (s, 1H, 5-H), 5.42 – 5.32 (m, 1H, 1-H), 4.92 (s, 2H, OC*H*$_2$-Ph), 4.56 (s, 1H, NH), 4.07 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH_3), 4.03 – 3.92 (m, 1H, 3-H), 3.89 (s, 3H, 3''-OCH_3), 3.81 (s, 3H, 6-OCH_3), 3.91 – 3.69 (m, 2H, OC*H*$_2$-CH_3), 3.78 (s, 3H, 4'-OCH_3), 3.60 (s, 3H, 7-OC*H*$_3$), 3.36 (q, *J* = 6.9 Hz, 2H, NC*H*$_2$-CH_2), 3.33 – 3.25 (m, 1H, 3-H), 3.13 (dd, *J* = 14.0, 3.8 Hz, 1H, α-H), 2.80 (dd, *J* = 14.1, 9.0 Hz, 2H, H-4, α-H), 2.72 (t, *J* = 7.1 Hz, 2H, NCH_2-C*H*$_2$), 2.50 (d, *J* = 16.4 Hz, 1H, H-4), 1.20 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.93 (br s, 3H, OCH_2-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 156.5 ('C=O), 155.4 (C=O), 152.6 (C-6), 149.5 (C-3''), 149.0 (C-4'), 148.7 (C-3'), 146.9 (C-4''), 145.4 C-8), 140.6 (C-7), 137.9 (C-1'''), 133.3 (C-1''), 132.3 (C-1'), 130.3 (C-4a), 128.4 (C-5''', C-3'''), 127.7 (C-4'''), 127.6 (C-6''', C-2'''), 124.2 (C-8a), 122.9 (C-6'), 121.0 (C-6''), 117.4 (C-2'), 115.6 (C-5''), 114.7 (C-2''), 113.6 (C-5'), 109.6 (C-5), 71.8 (O*C*H_2-Ph), 60.9 (O*C*H_2-CH_3), 60.7 ('O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.9 (4'-OCH_3 or

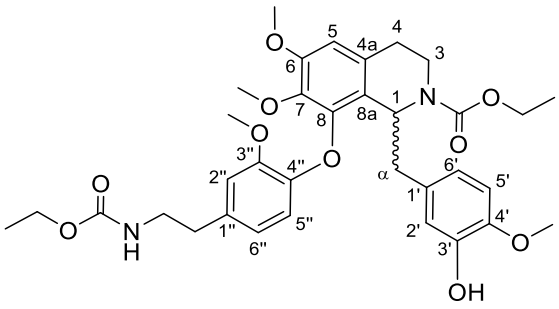
3''-OCH_3), 56.8 (4'-OCH_3 or 3''-OCH_3), 56.4 (6-OCH_3), 52.1 (C-1), 42.3 (NCH_2-CH_2), 39.9 (C-α), 37.7 (C-3), 35.9 (NCH_2-CH_2), 28.1 (C-4), 14.6 ('OCH_2-CH_3), 14.4 (OCH_2-CH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2936, 2832, 1690, 1606, 1509, 1424, 1330, 1255, 1212, 1154, 1131, 1108, 1069, 1023, 758

Purity (HPLC, method a) = 97% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{48}N_2O_{10} + H]^+$ 729.3382, found: 729.3385

(±)-8-(4-(2-((Ethoxycarbonyl)amino)ethyl)-2-methoxyphenoxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-hydroxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (59)



$C_{34}H_{42}N_2O_{10}$

M_W = 638.28 g/mol

To a solution of diaryl ether **58** (1.00 g, 1.37 mmol) in methanol (50 mL) palladium (10% on carbon, 100 mg, Pd 0.094 mmol) was added. The reaction was stirred for 12 h at ambient temperature under hydrogen atmosphere (1 atm). The catalyst was removed by passing the mixture through a small plug of celite, followed by washing with methanol (50 mL). The filtrate was concentrated *in vacuo* to give a white solid as desired product with no side products. The isolated product was used without purification for the following Pictet-Spengler cyclization.

yield: 805 mg, 1.26 mmol, 92%, white solid

mp: 61.5 – 62.0 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) δ [ppm] = 6.81 (d, *J* = 2.0 Hz, 1H, 2''-H), 6.66 (d, *J* = 8.2 Hz, 1H, 5'-H), 6.61 (d, *J* = 2.1 Hz, 1H, 2'-H), 6.57 (dd, *J* = 8.2, 2.0 Hz, 1H, 6''-H), 6.52 (d, *J* = 8.2 Hz, 1H, 5''-H), 6.52 – 6.48 (m, 2H, 5-H, 6'-H), 5.42 (s, 1H, OH), 5.36 (dd, *J* = 9.4 Hz, 1H, 1-H), 4.64 (s, 1H, NH), 4.07 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH$_3$), 4.08 – 3.94 (m, 1H, 3-H), 3.92 (s, 3H, 3''-OCH$_3$), 3.82 (s, 3H, 6-OCH$_3$), 3.79 (s, 3H, 4'-OCH$_3$), 3.87 – 3.66 (m, 2H, OC*H*$_2$-CH$_3$), 3.61 (s, 3H, 7-OCH$_3$), 3.37 (q, *J* = 7.0 Hz, 2H, NC*H*$_2$-CH$_2$), 3.39 – 3.28 (m, 1H, 3-H), 3.10 (dd, *J* = 14.0, 3.8 Hz, 1H, α-H), 2.89 – 2.78 (m, 1H, 4-H), 2.79 – 2.70 (m, 1H, α-H), 2.73 (t, *J* = 7.0 Hz, 2H, NCH$_2$-C*H*$_2$), 2.59 (d, *J* = 16.4 Hz, 1H, 4-H), 1.20 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.92 (br s, 3H, OCH$_2$-C*H*$_3$)

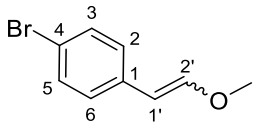
^{13}C NMR (101 MHz, TCl_2, 100 °C) δ [ppm] = 156.5 ('C=O), 155.4 (C=O), 152.6 (C-6), 149.5 (C-3''), 146.7 (C-4''), 145.5 (C-8), 145.4 (C-4'), 145.3 (C-3'), 140.7 (C-7), 133.2 (C-1''), 132.6 (C-1'), 130.1 (C-4a), 124.4 (C-8a), 121.0 (C-6'), 120.8 (C-6''), 116.1 (C-2'), 115.4 (C-5''), 114.4 (C-2''), 111.1 (C-5'), 109.8 (C-5), 60.9 (O*C*H$_2$-CH$_3$), 60.7 (7-OCH$_3$, 'O*C*H$_2$-CH$_3$, 56.7 (3''-OCH$_3$), 56.4 (6-OCH$_3$ or 4'-OCH$_3$), 56.3 (6-OCH$_3$ or 4'-OCH$_3$), 52.0 (C-1), 42.3 (N*C*H$_2$-CH$_2$), 39.8 (C-α), 37.5 (C-3), 35.9 (NCH$_2$-*C*H$_2$), 28.0 (C-4), 14.6 ('OCH$_2$-*C*H$_3$), 14.2 (OCH$_2$-*C*H$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3354, 2939, 1686, 1594, 1508, 1419, 1331, 1244, 1211, 1129, 1109, 1023, 960, 761

Purity (HPLC, method a) = 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{34}H_{41}N_2O_{10}]^-$ 637.2767, found: 637.2785

(*E/Z*)-4-Bromo-1-(2-methoxyvinyl)benzene (60)



C_9H_9BrO

M_W = 211.98 g/mol

Prepared from 4-Bromobenzaldehyde (2.00 g, 10.8 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, R_f = 0.23/0.30) to give the title compound as a colourless oil (2.06 g, 9.72 mmol, 90%, *E,Z*-isomer ratio 1:0.85, estimated by NMR integrals).

yield: 2.06 g, 9.67 mmol, 90%, colourless oil

NMR data of the major *E*-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.40 – 7.35 (m, 2H, 3-H, 5-H), 7.11 – 7.07 (m, 2H, 2-H, 6-H), 7.03 (d, *J* = 13.0 Hz, 1H, 2'-H), 5.74 (d, *J* = 13.0 Hz, 1H, 1'-H), 3.68 (s, 3H, OCH_3)

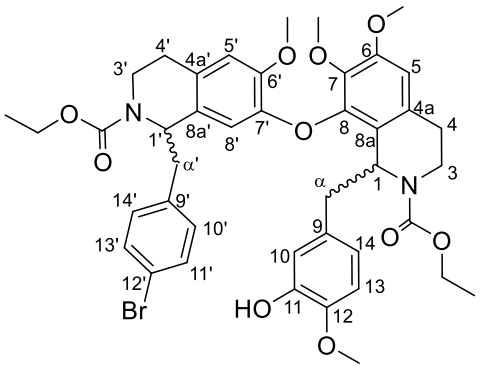
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 149.5 (C-2'), 135.5 (C-1), 131.3 (C-3, C-5), 126.8 (C-2, C-6), 119.1 (C-4), 104.2 (C-1'), 56.7 (OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2929, 2832, 1589, 1488, 1405, 1120, 1069, 1010, 816

Purity (HPLC, method a) = 76% (λ = 210 nm)

HRMS (EI): *m/z* calcd for $[C_9H_9{}^{79}BrO]^{\bullet+}$ 211.9831, found: 211.9827

(±)-8-((1-(4-Bromobenzyl)-*N*-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-hydroxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (61)



$C_{42}H_{47}BrN_2O_{10}$

M_W = 818.24 g/mol

Carbamate **59** (600 mg, 0.939 mmol) and enol ether **60** (240 mg, 1.13 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TFA as catalyst. The reaction was completed after 12 h. For separation of the racemic diastereomers of **61** 15% ethyl acetate in dichloromethane (R_f = 0.21 for the (1*R*,1'*R*)/(1*S*,1'*S*) isomers (**61a**) and 0.30 for the (1*R*,1'*S*)/(1*S*,1'*R*) isomers (**61b**)) was used.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers **61a**:

yield: 385 mg, 0.471 mmol, 50%, white solid

mp: 73.0 – 75.0 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) *δ* [ppm] = δ 7.23 – 7.18 (m, 2H, 13'-H, 11'-H), 6.86 – 6.80 (m, 2H, 14'-H, 10'-H), 6.70 (s, 1H, 5'-H), 6.67 (d, *J* = 8.1 Hz, 1H, 13-H), 6.63 (d, *J* = 2.0 Hz, 1H, 10-H), 6.55 (s, 1H, 5-H), 6.50 (dd, *J* = 8.2, 2.1 Hz, 1H, 14-H), 6.22 (s, 1H, 8'-H), 5.35 (s, 2H, 1-H, OH), 5.05 (t, *J* = 6.3 Hz, 1H, 1'-H), 4.13 – 4.04 (m, 1H, 3-H), 4.01 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH$_3$), 3.97 – 3.89 (m, 1H, 3'-H), 3.91 (s, 3H, 6'-OCH$_3$), 3.85 (s, 3H, 6-OCH$_3$), 3.87 – 3.66 (m, 2H, OC*H*$_2$-CH$_3$), 3.80 (s, 3H, 12-OCH$_3$), 3.61 (s, 3H, 7-OCH$_3$), 3.40 – 3.30 (m, 1H, 3-H), 3.23 – 3.12 (m, 1H, 3'-H), 2.98 (dd, *J* = 14.0, 3.6 Hz, 1H, α-H), 2.92 – 2.81 (m, 1H, 4-H), 2.86 (dd, *J* = 6.4, 3.5 Hz, 2H, α'-H), 2.81 – 2.73 (m, 1H, 4'-H), 2.70 (dd, *J* = 13.9, 10.0 Hz, 1H, α-H), 2.62 (d, *J* = 16.3 Hz, 1H, 4-H), 2.53 (dt, *J* = 16.0, 4.6 Hz, 1H, 4'-H), 1.14 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.92 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, TCl_2, 100 °C) *δ* [ppm] = 155.4 (C=O), ('C=O), 152.5 (C-6), 148.4 (C-6'), 146.2 (C-7'), 145.5 (C-11), 145.4 (C-12), 145.0 (C-8), 140.6 (C-7), 137.4 (C-9'), 132.6 (C-9), 131.2 (C-14', C-10'), 131.1 (C-13', C-11'), 130.0 (C-4a), 128.8 (C-8a'), 128.3 (C-4a'), 124.3 (C-8a), 121.0 (C-14), 120.2 (C-12'), 116.0 (C-10), 114.0 (C-8'), 113.7 (C-5'), 111.0 (C-13), 110.1

(C-5), 61.2 ('O*C*H_2-CH_3), 60.9 (O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.6 (6'-OCH_3), 56.5 (6-OCH_3), 56.4 (12-OCH_3), 55.6 (C-1'), 52.0 (C-1), 42.6 (C-α'), 39.8 (C-α), 38.9 (C-3'), 37.3 (C-3), 28.2 (C-4'), 28.0 (C-4), 14.6 ('OCH_2-*C*H_3), 14.2 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3527, 2923, 2853, 1686, 1607, 1508, 1426, 1330, 1237, 1196, 1120, 1068, 1024, 804, 760

Purity (HPLC, method a) = 92% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for [$C_{42}H_{47}{}^{79}BrN_2O_{10}$ + H]$^+$ 819.2487, found: 819.2479

(1*R*,1'*S*)/(1*S*,1'*R*) isomers **61b**:

yield: 354 mg, 0.433 mmol, 46%, white solid

mp: 89.0 – 90.0 °C

^{1}H NMR (400 MHz, TcI_2, 100 °C) δ [ppm] = 7.24 – 7.18 (m, 2H, 13'-H, 11'-H), 6.88 – 6.82 (m, 2H, 14'-H, 10'-H), 6.69 (s, 1H, 5'-H), 6.68 (d, *J* = 2.1 Hz, 1H, 10-H), 6.67 (d, *J* = 8.2 Hz, 1H, 13-H), 6.55 (s, 1H, 5-H), 6.53 (dd, *J* = 8.4, 1.9 Hz, 1H, 14-H), 6.16 (s, 1H, 8'-H), 5.38 (s, 1H, O*H*), 5.32 (dd, *J* = 9.7, 3.2 Hz, 1H, 1-H), 5.03 (t, *J* = 6.2 Hz, 1H, 1'-H), 4.13 – 3.93 (m, 4H, 3-H, 3'-H, 'OC*H*$_2$-CH_3), 3.90 (s, 3H, 6'-OCH_3), 3.84 (s, 3H, 6-OCH_3), 3.86 – 3.74 (m, 2H, OC*H*$_2$-CH_3), 3.80 (s, 3H, 12-OCH_3), 3.62 (s, 3H, 7-OCH_3), 3.42 – 3.31 (m, 1H, 3-H), 3.22 – 3.08 (m, 2H, α-H, 3'-H), 2.98 – 2.87 (m, 1H, 4-H), 2.85 (dd, *J* = 6.3, 3.4 Hz, 2H, α'-H), 2.84 – 2.71 (m, 2H, α-H, 4'-H), 2.64 (d, *J* = 16.2 Hz, 1H, 4-H), 2.53 (dt, *J* = 16.0, 4.4 Hz, 1H, 4'-H), 1.14 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.95 (br s, 3H, OCH_2-C*H*$_3$)

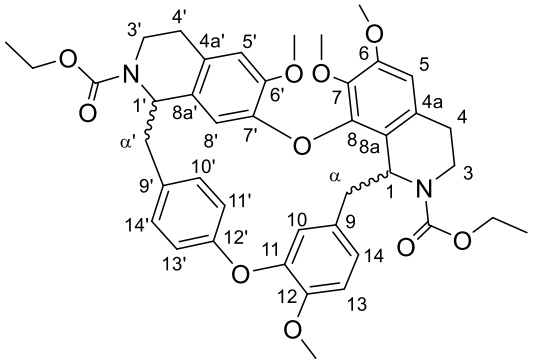
^{13}C NMR (101 MHz, TcI_2, 100 °C) δ [ppm] = 155.4 (C=O, 'C=O), 152.4 (C-6), 148.3 (C-6'), 146.1 (C-7'), 145.5 (C-8), 145.4 (C-12), 145.0 (C-11), 140.7 (C-7), 137.6 (C-9'), 132.6 (C-9), 131.2 (C-14', C-10'), 131.1 (C-13', C-11'), 130.0 (C-4a), 128.9 (C-8a'), 128.1 (C-4a'), 124.2 (C-8a), 121.1 (C-14), 120.1 (C-12'), 116.1 (C-10), 113.6 (C-5', C-8'), 111.0 (C-13), 110.2 (C-5), 61.2 ('O*C*H_2-CH_3), 60.9 (O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.6 (6-OCH_3 or 6'-OCH_3), 56.5 (6-OCH_3 or 6'-OCH_3), 56.3 (12-OCH_3), 55.7 (C-1'), 52.0 (C-1), 42.7 (C-α'), 39.8 (C-α), 38.7 (C-3'), 37.5 (C-3), 28.3 (C-4'), 28.1 (C-4), 14.6 ('OCH_2-*C*H_3), 14.3 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3438, 2931, 2840, 1692, 1609, 1510, 1427, 1332, 1237, 1201, 1122, 1069, 1026, 804, 760

Purity (HPLC, method a) = 96% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for [$C_{42}H_{47}{}^{79}BrN_2O_{10}$ + H]$^+$ 819.2487, found: 819.2480

(±)-*N,N'*-Bis-(ethoxycarbonyl)-nortetrandrine and isomers (62)



$C_{42}H_{46}N_2O_{10}$

M_W = 738.32 g/mol

Via routes 1a and 1b – Preparation cyclization *via intra*molecular Ullmann-type C–O coupling reaction:

Previously separated diastereomers of bisbenzylisoquinoline **61** (200 mg, 0.244 mmol of pure diastereomer) or of bisbenzylisoquinoline **68**, respectively (200 mg, 0.244 mmol of pure diastereomer) were reacted following General Procedure 3 (*intra*molecular C–O coupling). The reactions were completed after 52 h. Purification was accomplished by flash column chromatography (35% acetone in hexanes, R_f = 0.29) and the products obtained as beige solids.

Yields obtained from bisbenzylisoquinoline **61**: (1*R*,1'*R*)/(1*S*,1'*S*) isomers: 115 mg, 0.156 mmol, 64%; (1*R*,1'*S*)/(1*S*,1'*R*) isomers: 112 mg, 0.152 mmol, 62%.

Yields obtained from bisbenzylisoquinoline **68**: (1*R*,1'*R*)/(1*S*,1'*S*) isomers: 91.9 mg, 0.124 mmol, 51%; (1*R*,1'*S*)/(1*S*,1'*R*) isomers: 63.1 mg, 0.0854 mmol, 35%.

Via routes 2a and 2b – Preparation by *intra*molecular *N*-acyl Pictet-Spengler reaction:

Enol ether **69** or enol ether **70**, respectively (50.0 mg, 0.0649 mmol) were reacted following General Procedure 2 (*intra*molecular *N*-acyl Pictet-Spengler reaction). The reactions were completed after 12 h. Purification was accomplished by flash column chromatography (35% acetone in hexanes, R_f = 0.29). Yield obtained from enol ether **69**: 13.5 mg, 0.0183 mmol, 28%; yield obtained from enol ether **70**: 38.0 mg, 0.0514 mmol, 79%.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers **62a**:

mp: 132.0 – 134.0 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) δ [ppm] = 7.38 (d, *J* = 8.2 Hz, 1H, 14'-H or 10'-H), 7.12 (dd, *J* = 8.2, 2.5 Hz, 1H, 13'-H or 11'-H), 6.79 (d, *J* = 8.1 Hz, 1H, 13-H), 6.67 (s, 1H, 13'-H or 11'-H), 6.64 (s, 1H, 5'-H), 6.56 (dd, *J* = 8.1, 2.0 Hz, 1H, 14-H), 6.47 (d, *J* = 1.9 Hz, 1H, 10-H), 6.32 (s,

1H, 5-H), 6.19 (dd, *J* = 8.4, 2.2 Hz, 1H, 14'-H or 10'-H), 6.16 (s, 1H, 8'-H), 5.26 (t, *J* = 6.1 Hz, 1H, 1-H), 5.04 (s, 1H, 1'-H), 4.36 – 4.20 (m, 3H, H-3, 'OC*H*$_2$-CH$_3$), 4.03 – 3.95 (m, 1H, 3'-H), 3.87 (s, 3H, 12-OCH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.89 – 3.59 (m, 2H, OC*H*$_2$-CH$_3$), 3.53 – 3.37 (m, 3H, 3-H, 3'-H, α'-H), 3.34 (s, 3H, 6'-OCH$_3$), 3.26 (s, 3H, 7-OCH$_3$), 3.19 – 3.07 (m, 1H, 4'-H), 2.94 – 2.75 (m, 2H, H-4, 4'-H), 2.71 (d, *J* = 5.9 Hz, 2H, α-H), 2.69 – 2.59 (m, 2H, 4-H, α'-H), 1.36 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.86 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl$_2$, 100 °C) *δ* [ppm] = 155.9 ('C=O), 155.6 (C=O), 154.3 (C-12'), 152.0 (C-6), 150.2 (C-11), 149.1 (C-6'), 147.9 (C-12), 147.0 (C-8), 144.9 (C-7'), 138.9 (C-7), 134.6 (C-9'), 133.8 (C-9), 132.2 (C-14' or C-10'), 130.1 (C-14' or C-10'), 130.0 (C-4a'), 128.8 (C-8a'), 128.1 (C-4a), 122.9 (C-8a), 122.0 (C-13' or C-11'), 121.9 (C-14), 121.5 (C-13' or C-11'), 119.6 (C-8'), 116.8 (C-10), 114.1 (C-5'), 113.6 (C-13), 107.4 (C-5), 61.4 , ('O*C*H$_2$-CH$_3$), 60.7 (O*C*H$_2$-CH$_3$), 60.3 (7-OCH$_3$), 57.7 (C-1'), 57.1 (12-OCH$_3$ or 6'-OCH$_3$), 57.0 (12-OCH$_3$ or 6'-OCH$_3$), 56.3 (6-OCH$_3$), 53.5 (C-1), 41.9 (C-3', C-α'), 40.9 (C-α), 36.6 (C-3), 28.0 (C-4), 27.8 (C-4'), 14.8 ('OCH$_2$-*C*H$_3$), 14.2 (OCH$_2$-*C*H$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2940, 2832, 1687, 1585, 1507, 1417, 1330, 1277, 1252, 1230, 1207, 1123, 1097, 1024, 841, 768

Purity (HPLC, method a) = 94% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for [C$_{42}$H$_{46}$N$_2$O$_{10}$ + H]$^+$ 739.3225, found: 739.3223

(1*R*,1'*S*)/(1*S*,1'*R*) isomers **62b**:

mp: 142.5 – 144.0 °C

^{1}H NMR (400 MHz, Tcl$_2$, 100 °C) *δ* [ppm] = 7.40 – 7.33 (m, 1H, 14'-H or 10'-H), 7.07 (dd, *J* = 8.2, 2.5 Hz, 1H, 13'-H or 11'-H), 6.76 (d, *J* = 8.0 Hz, 1H, 13-H), 6.66 – 6.60 (m, 2H, 5', 13'-H or 11'-H), 6.57 (dd, *J* = 8.0, 2.0 Hz, 1H, 14-H), 6.42 – 6.36 (m, 1H, 14'-H or 10'-H), 6.32 (s, 1H, 10-H), 6.28 (s, 1H, 5-H), 6.17 (s, 1H, 8'-H), 5.26 (d, *J* = 8.7 Hz, 1H, 1-H), 5.10 (dd, *J* = 10.5, 6.2 Hz, 1H, 1'-H), 4.33 – 4.07 (m, 3H, 3-H, 'OC*H*$_2$-CH$_3$), 3.96 – 3.89 (m, 1H, 3'-H), 3.87 (s, 3H, 12-OCH$_3$), 3.85 – 3.77 (m, 2H, OC*H*$_2$-CH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.61 (s, 3H, 6'-OCH$_3$), 3.57 – 3.42 (m, 2H, 3'-H, α'-H), 3.38 – 3.25 (m, 1H, 3-H), 3.16 (s, 3H, 7-OCH$_3$), 3.15 – 3.08 (m, 2H, α-H, 4'-H), 2.82 (dt, *J* = 15.8, 4.7 Hz, 1H, 4'-H), 2.77 – 2.67 (m, 2H, 4-H, α'-H), 2.55 (dd, *J* = 13.9, 9.5 Hz, 1H, α-H), 2.50 – 2.35 (m, 1H, 4-H), 1.33 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 1.00 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl$_2$, 100 °C) *δ* [ppm] = 155.8 (C=O), 155.5 ('C=O), 154.4 (C-12'), 152.5 (C-6), 150.4 (C-11), 150.1 (C-6'), 147.9 (C-12), 144.4 (C-7'), 137.9 (C-7), 134.8 (C-9'), 134.0 (C-9), 131.5 (C-14' or C-10'), 130.4 (C-4a'), 130.0 (C-14' or C-10'), 129.6 (C-4a), 128.3 (C-8a'),

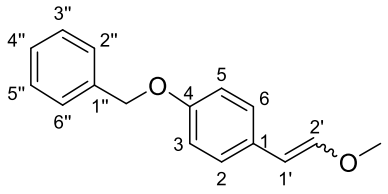
122.1 (C-14, C-13' or 11'), 122.0 (C-13' or C-11'), 120.6 (C-8a), 119.6 (C-8'), 117.1 (C-10), 113.3 (C-13), 111.9 (C-5'), 106.9 (C-5), 61.3 ('O*C*H_2-CH_3), 60.9 (O*C*H_2-CH_3), 60.5 (7-OCH_3), 57.1 (12-OCH_3), 1', 56.3 (6-OCH_3), 56.1 (6'-OCH_3), 54.1 (C-1), 41.7 (C-3'), 41.6 (C-α'), 39.0 (C-α), 28.2 (C-4), 28.1 (C-4'), 14.8 ('OCH_2-*C*H_3), 14.3 (OCH_2-*C*H_3). The resonances of C-3 and C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2929, 2839, 1693, 1584, 1505, 1417, 1330, 1276, 1255, 1231, 1204, 1124, 1101, 1020, 842, 770

Purity (HPLC, method a) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{46}N_2O_{10} + H]^+$ 739.3225, found: 739.3225

(*E/Z*)-4-(Benzyloxy)-1-(2-methoxyvinyl)benzene (63)



$C_{16}H_{16}O_2$

M_W = 240.11 g/mol

Obtained from 4-benzyloxybenzaldehyde (5.00 g, 23.6 mmol) following General Procedure 1 (Wittig olefination). Purification by flash column chromatography (5% ethyl acetate in hexanes, R_f = 0.32) gave the title compound as a white solid (*E,Z*-isomer ratio 1:1.4, estimated by NMR-integrals).

yield: 5.50 g, 22.9 mmol, 97%, white solid

mp: 37.5 °C

NMR data of the major *Z*-isomer:
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.55 – 7.48 (m, 2H, 6-H, 2-H), 7.46 – 7.41 (m, 2H, 2''-H, 6''-H), 7.41 – 7.35 (m, 2H, 3''-H, 5''-H), 7.35 – 7.29 (m, 1H, 4''-H), 6.93 – 6.87 (m, 2H, 3-H, 5-H), 6.06 (d, *J* = 7.0 Hz, 1H, 2'-H), 5.18 (d, *J* = 7.0 Hz, 1H, 1'-H), 5.06 (s, 2H, OCH_2-Ph), 3.76 (s, 3H, OCH_3)

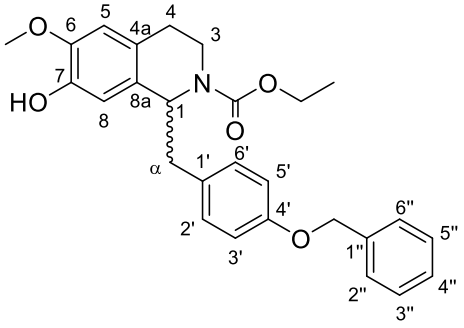
^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 156.9 (C-4), 146.6 (C-2'), 137.3 (C-1''), 129.5 (C-6, C-2), 129.2 (C-1), 128.7 (C-3'', C-5''), 128.0 (C-4''), 127.6 (C-2'', C-6''), 114.8 (C-3, C-5), 105.3 (C-1'), 70.1 (OCH_2-Ph), 60.6 (OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3034, 2834, 2080, 1639, 1606, 1236, 1093, 836, 739

Purity (HPLC, method a) = 96% (λ = 210 nm)

HRMS (EI): *m/z* calcd for $[C_{16}H_{16}O_2]^{\bullet+}$ 240.1145, found: 240.1140

(±)-*N*-Ethoxycarbonyl-7-hydroxy-6-methoxy-1-(4'-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline (64)



$C_{27}H_{29}NO_5$

M_W = 447.20 g/mol

Carbamate **57** (0.950 g, 3.97 mmol) and enol ether **63** (1.43 g, 5.96 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TFA as catalyst. The reaction was completed after 12 h. Purification by flash column chromatography (5% ethyl acetate in dichloromethane, R_f = 0.29) gave **64** as a white solid.

yield: 1.71 g, 3.81 mmol, 96%, white solid

mp: 45.5 – 48.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.41 – 7.37 (m, 2H, 2''-H, 6''-H), 7.37 – 7.31 (m, 2H, 3''-H, 5''-H), 7.30 – 7.25 (m, 1H, 4''-H), 7.00 – 6.94 (m, 2H, 2'-H, 6'-H), 6.88 – 6.83 (m, 2H, 3'-H, 5'-H), 6.58 – 6.52 (m, 2H, 8-H, 5-H), 5.33 (s, 1H, OH), 5.14 (t, *J* = 6.7 Hz, 1H, 1-H), 5.02 (s, 2H, OC*H*$_2$-Ph), 4.04 – 3.88 (m, 3H, H-3, OC*H*$_2$-CH_3), 3.84 (s, 3H, 6-OCH_3), 3.22 (ddd, *J* = 13.7, 9.9, 4.6 Hz, 1H, 3-H), 2.97 (d, *J* = 6.6 Hz, 2H, α-H), 2.76 (ddd, *J* = 15.9, 9.9, 5.9 Hz, 1H, 4-H), 2.51 (dt, *J* = 15.8, 4.4 Hz, 1H, 4-H), 1.10 (t, *J* = 7.1 Hz, 3H, OCH_2-C*H*$_3$)

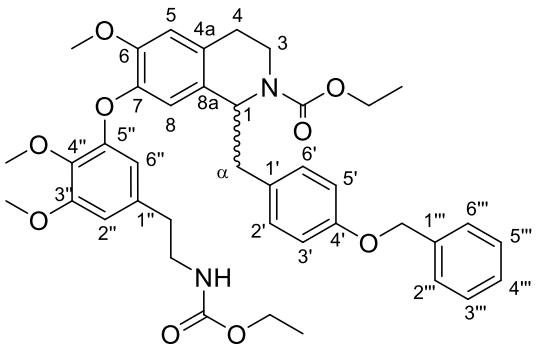
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 157.8 (C-4'), 155.5 (C=O), 145.7 (C-6), 144.1 (C-7), 137.6 (C-1''), 131.1 (C-1'), 130.6 (C-2', C-6'), 130.0 (C-8a), 128.5 (C-3'', C-5''), 127.8 (C-4''), 127.4 (C-2'', C-6''), 126.1 (C-4a), 115.2 (C-3', C-5'), 113.4 (C-8), 111.3 (C-5), 70.5 (O*C*H$_2$-Ph), 61.1 (O*C*H$_2$-CH_3), 56.3 (6-OCH_3), 56.1 (C-1), 42.1 (C-α), 38.5 (C-3), 28.2 (C-4), 14.6 (OCH_2-*C*H$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3032, 2929, 2360, 1683, 1509, 1428, 1232, 1201, 1098, 1014, 696

Purity (HPLC, method a) = 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{27}H_{29}NO_5 + H]^+$ 448.2118, found: 448.2120

(±)-7-(5-(2-((Ethoxycarbonyl)amino)ethyl)-2,3-dimethoxyphenoxy)-*N*-ethoxycarbonyl-6-methoxy-1-(4'-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline (65)



$C_{40}H_{46}N_2O_9$

M_W = 698.32 g/mol

Phenol intermediate **64** (1.70 g, 3.80 mmol) and aryl bromide **53** (1.51 g, 4.56 mmol) were coupled following General Procedure 3 (*inter*molecular C–O coupling reaction). The reaction was completed after 3 days. Purification by flash column chromatography (30% acetone in hexanes, R_f = 0.30) affording the product as a beige solid.

yield: 1.69 g, 2.42 mmol, 64%, beige solid

mp: 46.5 – 48.0 °C

^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.40 – 7.36 (m, 2H, 2'''-H, 6'''-H), 7.33 (t, *J* = 7.3 Hz, 2H, 3'''-H, 5'''-H), 7.30 – 7.24 (m, 1H, 4'''-H), 6.94 – 6.90 (m, 2H, 2'-H, 6'-H), 6.82 – 6.77 (m, 2H, 3'-H, 5'-H), 6.68 (s, 1H, 5-H), 6.50 (s, 1H, 8)-H, 6.45 (d, *J* = 1.9 Hz, 1H, 2''-H), 6.20 (d, *J* = 1.9 Hz, 1H, 6''-H), 5.12 (t, *J* = 6.5 Hz, 1H, 1-H), 4.98 (s, 2H, OC*H*$_2$-Ph), 4.49 (s, 1H, NH), 4.04 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH_3), 4.03 – 3.92 (m, 3H, 3-H, OC*H*$_2$-CH_3), 3.83 (s, 3H, 3''-OCH_3), 3.79 (s, 3H, 4''-OCH_3), 3.78 (s, 3H, 6-OCH_3), 3.30 (q, *J* = 6.8 Hz, 2H, NC*H*$_2$-CH_2), 3.23 (ddd, *J* = 13.6, 9.7, 4.6 Hz, 1H, 3-H), 2.94 (tt, *J* = 13.7, 7.2 Hz, 2H, α-H), 2.81 (ddd, *J* = 15.8, 9.7, 5.9 Hz, 1H, 4-H), 2.64 (t, *J* = 7.1 Hz, 2H, NCH_2-C*H*$_2$), 2.61 – 2.52 (m, 1H, 4-H), 1.18 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 1.13 (t, *J* = 7.0 Hz, 3H, OCH_2-C*H*$_3$)

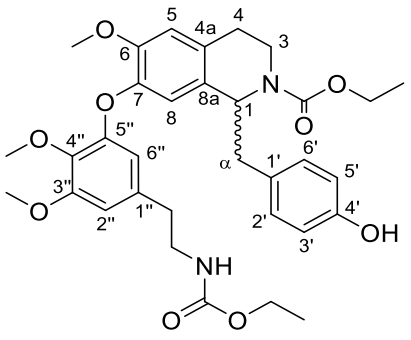
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 157.8 (C-4'), 156.4 ('C=O), 155.5 (C=O), 154.0 (C-3''), 151.1 (C-5''), 149.9 (C-6), 144.4 (C-7), 139.0 (C-4''), 137.5 (C-1'''), 134.1 (C-1''), 130.8 (C-1'), 130.6 (C-2', C-6'), 130.5 (C-8a), 129.8 (C-4a), 128.5 (C-3''', C-5'''), 127.8 (C-4'''), 127.4 (C-2''', C-6'''), 119.0 (C-8), 115.1 (C-3', C-5'), 114.1 (C-5), 111.5 (C-6''), 108.6 (C-2''), 70.5 (O*C*H_2-Ph), 61.2 (O*C*H_2-CH_3), 60.9 (4''-OCH_3), 60.7 ('O*C*H_2-CH_3), 56.7 (3''-OCH_3), 56.6 (6-OCH_3), 55.9 (C-1), 42.2 (N*C*H_2-CH_2), 42.1 (C-α), 38.5 (C-3), 36.2 (NCH_2-*C*H_2), 28.4 (C-4), 14.6 ('OCH_2-*C*H_3, OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2923, 2849, 1686, 1583, 1508, 1424, 1231, 1102, 1012, 824, 764, 736

Purity (HPLC, method a) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{40}H_{46}N_2O_9 + H]^+$ 699.3276, found: 699.3277

(±)-7-(5-(2-((Ethoxycarbonyl)amino)ethyl)-2,3-dimethoxyphenoxy)-*N*-ethoxycarbonyl-6-methoxy-1-(4'-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (66)



$C_{33}H_{40}N_2O_9$

M_W = 608.27 g/mol

To a solution of diaryl ether **65** (1.69 g, 2.42 mmol) in methanol (50 mL) palladium (10% on carbon, 169 mg, Pd 1.59 mmol) was added. The mixture was stirred for 12 h at ambient temperature under hydrogen atmosphere (1 atm). The catalyst was removed by filtration through a small plug of celite, followed by washing with methanol (50 mL). The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (35% acetone in hexanes, R_f = 0.22) gave the title compound as a white solid.

yield: 1.38 g, 2.27 mmol, 94%, white solid

mp: 63.0 – 65.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.85 – 6.80 (m, 2H, 2'-H, 6'-H), 6.68 (s, 1H, 5-H), 6.66 – 6.62 (m, 2H, 3'-H, 5'-H), 6.45 (d, *J* = 1.9 Hz, 1H, 2''-H), 6.30 (s, 1H, 8-H), 6.19 (d, *J* = 1.9 Hz, 1H, 6''-H), 5.49 (s, 1H, OH), 5.04 (t, *J* = 6.6 Hz, 1H, 1-H), 4.61 (t, *J* = 5.7 Hz, 1H, NH), 4.08 (q, *J* = 7.1 Hz, 4H, OC*H*$_2$-CH$_3$, 'OC*H*$_2$-CH$_3$), 3.95 – 3.85 (m, 1H, 3-H), 3.84 (s, 3H, 3''-OCH$_3$), 3.78 (s, 3H, 6-OCH$_3$), 3.76 (s, 3H, 4''-OCH$_3$), 3.36 – 3.27 (m, 3H, H-3, NC*H*$_2$-CH$_2$), 2.99 (dd, *J* = 13.5, 5.9 Hz, 1H, α-H), 2.86 – 2.76 (m, 2H, 4-H, α-H), 2.68 – 2.61 (m, 3H, 4-H, NCH$_2$-C*H*$_2$), 1.23 – 1.17 (m, 6H, OCH$_2$-C*H*$_3$, 'OCH$_2$-C*H*$_3$)

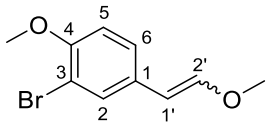
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 156.8 ('C=O), 155.5 (C=O), 154.7 (C-4'), 154.0 (C-3''), 150.8 (C-5''), 149.7 (C-6), 144.7 (C-7), 139.2 (C-4''), 133.9 (C-1''), 130.7 (C-2', C-6'), 130.1 (C-4a, C-1'), 129.5 (C-8a), 118.6 (C-8), 115.3 (C-3', C-5'), 114.0 (C-5), 112.2 (C-6''), 108.9 (C-2''), 61.2 ('O*C*H$_2$-CH$_3$ or O*C*H$_2$-CH$_3$), 61.0 ('O*C*H$_2$-CH$_3$ or O*C*H$_2$-CH$_3$), 60.8 (4''-OCH$_3$), 56.7 (3''-OCH$_3$), 56.6 (6-OCH$_3$), 56.3 (C-1), 42.2 (C-α, N*C*H$_2$-CH$_2$), 39.1 (C-3), 36.2 (NCH$_2$-*C*H$_2$), 28.4 (C-4), 14.7 (OCH$_2$-*C*H$_3$ or 'OCH$_2$-*C*H$_3$), 14.6 (OCH$_2$-*C*H$_3$ or 'OCH$_2$-*C*H$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2833, 2362, 1689, 1508, 1425, 1230, 1100, 1007, 773

Purity (HPLC, method a) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for [$C_{33}H_{40}N_2O_9$+ H]$^+$ 609.2807, found: 609.2810

(*E/Z*)-3-Bromo-4-methoxy-1-(2-methoxyvinyl)benzene (67)



$C_{10}H_{11}BrO_2$

M_W = 241.99 g/mol

Obtained from 3-bromo-4-methoxybenzaldehyde (0.500 g, 2.33 mmol) following General Procedure 1 (Wittig olefination). Purification by flash column chromatography (5% ethyl acetate in hexanes, R_f = 0.30) affording the product as a colourless oil (*E,Z*-isomer ratio 1:0.91 estimated by NMR-integrals).

yield: 0.455 g, 1.87 mmol, 80%, colourless oil

NMR data of the major *E*-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.46 – 7.41 (m, 1H, 2-H), 7.11 (dd, *J* = 8.5, 2.2 Hz, 1H, 6-H), 6.93 (d, *J* = 12.9 Hz, 1H, 2'-H), 6.82 (d, *J* = 5.1 Hz, 1H, 5-H), 5.71 (d, *J* = 12.9 Hz, 1H, 1'-H), 3.87 (s, 3H, 4-OCH_3), 3.67 (s, 3H, 2'-OCH_3)

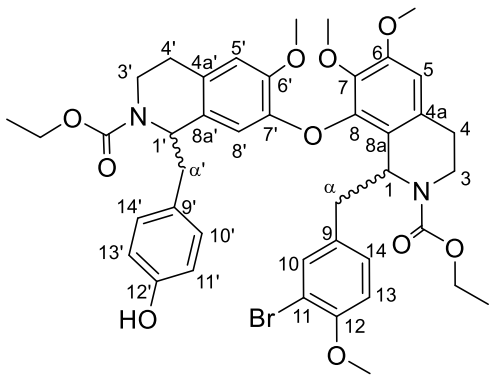
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 154.1 (C-4), 148.6 (C-2'), 130.7 (C-1), 129.9 (C-2), 125.3 (C-6), 112.3 (C-5), 111.5 (C-3), 103.6 (C-1'), 56.7 (2'-OCH_3), 56.5 (4-OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2937, 2837, 2074, 1640, 1496, 1253, 1095, 1053, 816

Purity (HPLC, method a) = 92% (λ = 210 nm)

HRMS (EI): *m/z* calcd for $[C_{10}H_{11}{}^{79}BrO_2]^{\bullet+}$ 241.9937, found: 241.9938

(±)-8-((1-(4-Hydroxybenzyl)-*N*-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-bromo-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (68)



$C_{42}H_{47}BrN_2O_{10}$

M_W = 818.24 g/mol

Intermediate **66** (200 mg, 0.329 mmol) and enol ether **67** (96.0 mg, 0.394 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TFA as catalyst to give a racemic mixture of diastereomers of tetrahydroisoquinoline **68** in a ratio of 62:38 (*R,R*)/(*S,S*):(*S,R*)/(*R,S*). The reaction was completed after 12 h. Purification and separation of the diastereomers was accomplished by flash column chromatography (20% ethyl acetate in dichloromethane, R_f = 0.17 ((1*R*,1'*S*)/(1*S*,1'*R*) isomers (**68b**) and 0.13 (1*R*,1'*R*)/(1*S*,1'*S*) isomers (**68a**)) to give both diasereomers as white solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers **68a**:

yield: 113 mg, 0.138 mmol, 42%, white solid

mp: 68.5 – 70.5 °C

^{1}H NMR (400 MHz, TcI_2, 100 °C) *δ* [ppm] = 7.18 (d, *J* = 2.1 Hz, 1H, 10-H), 6.91 (dd, *J* = 8.3, 2.1 Hz, 1H, 14-H), 6.81 – 6.76 (m, 2H, 14'-H, 10'-H), 6.74 – 6.68 (m, 2H, 13-H, 5'-H), 6.58 – 6.52 (m, 3H, 5-H, 13'-H, 11'-H), 6.21 (s, 1H, 8'-H), 5.30 (d, *J* = 10.1 Hz, 1H, 1-H), 5.02 (t, *J* = 6.5 Hz, 1H, 1'-H), 4.86 (s, 1H, OH), 4.14 – 4.04 (m, 1H, 3-H), 4.00 (q, *J* = 7.3 Hz, 2H, 'OC*H*$_2$-CH$_3$), 3.91 (s, 3H, 6'-OCH$_3$), 3.96 – 3.89 (m, 1H, 3'-H), 3.85 (s, 3H, 6-OCH$_3$), 3.87 – 3.71 (m, 2H, OC*H*$_2$-CH$_3$), 3.79 (s, 3H, 12-OCH$_3$), 3.63 (s, 3H, 7-OCH$_3$), 3.37 – 3.28 (m, 1H, 3-H), 3.18 (ddd, *J* = 13.4, 9.5, 4.4 Hz, 1H, 3'-H), 3.05 (dd, *J* = 14.1, 3.7 Hz, 1H, α-H), 2.88 (d, *J* = 6.4 Hz, 1H, 4-H), 2.84 (t, *J* = 6.4 Hz, 2H, α'-H), 2.75 (td, *J* = 16.2, 14.4, 9.9 Hz, 2H, α-H, 4'-H), 2.61 (d, *J* = 6.3 Hz, 1H, 4-H), 2.55 (td, *J* = 11.3, 5.5 Hz, 1H, 4'-H), 1.14 (t, *J* = 7.0 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.89 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR, HSQC, HMBC (101 MHz, TcI_2, 100 °C) *δ* [ppm] = 155.5 ('C=O), 155.4 (C=O), 154.8 (C-12), 154.3 (C-12'), 152.6 (C-6), 148.2 (C-6'), 146.0 (C-7'), 145.0 (C-8), 140.8 (C-7), 134.2 (C-10), 133.2 (C-9), 130.5 (C-14', C-10'), 130.4 (C-9'), 130.0 (C-8a), 129.4 (C-14), 129.2 (C-8a'), 128.5 (C-4a'), 123.9 (C-4a), 115.3 (C-13', C-11'), 114.1 (C-8'), 113.5 (C-5'), 112.5 (C-13),

111.7 (C-11), 110.1 (C-5), 61.2 ('O*C*H_2-CH_3), 61.1 (O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.7 (6-, 6'- or 12-OCH_3), 56.6 (6-, 6'- or 12-OCH_3), 56.6 (6-, 6'- or 12-OCH_3), 55.9 (C-1'), 52.0 (C-1), 42.1 (C-α'), 39.2 (C-α), 38.7 (C-3'), 37.4 (C-3), 28.3 (C-4'), 28.0 (C-4), 14.6 ('OCH_2-*C*H_3), 14.2 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2918, 2850, 2366, 1668, 1612, 1497, 1427,1331, 1255, 1120, 1020, 887, 742

Purity (HPLC, method a) = 75% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{47}{}^{79}BrN_2O_{10} + H]^+$ 819.2492, found: 819.2500

(1*R*,1'*S*)/(1*S*,1'*R*) isomers **68b**:

yield: (70.5 mg, 0.0856 mmol, 26%.

mp: 71.5 – 73.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.24 (d, *J* = 2.1 Hz, 1H, 10-H), 6.94 (dd, *J* = 8.3, 2.1 Hz, 1H, 14-H), 6.77 (d, *J* = 8.4 Hz, 2H, 14'-H, 10'-H), 6.74 (d, *J* = 8.3 Hz, 1H, 13-H), 6.70 (s, 1H, 5'-H), 6.56 (d, *J* = 8.3 Hz, 2H, 13'-H, 11'-H), 6.51 (s, 1H, 5-H), 6.11 (s, 1H, 8'-H), 5.27 (d, *J* = 8.3 Hz, 1H, 1-H), 5.10 (s, 1H, OH), 4.99 (t, *J* = 6.5 Hz, 1H, 1'-H), 4.01 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH_3), 4.07 – 3.89 (m, 2H, 3-H, 3'-H), 3.90 (s, 3H, 6'-OCH_3), 3.86 – 3.78 (m, 2H, OC*H*$_2$-CH_3), 3.83 (s, 3H, 6-OCH_3), 3.80 (s, 3H, 12-OCH_3), 3.59 (s, 3H, 7-OCH_3), 3.40 – 3.31 (m, 1H, 3'-H), 3.25 (d, *J* = 15.6 Hz, 1H, 3-H), 3.17 (dd, *J* = 14.1, 3.9 Hz, 1H, α-H), 2.92 – 2.73 (m, 5H, 4-H, α-H, 4'-H, α'-H), 2.62 – 2.52 (m, 2H, 4-H, 4'-H), 1.15 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.97 (br s, 3H, OCH_2-C*H*$_3$)

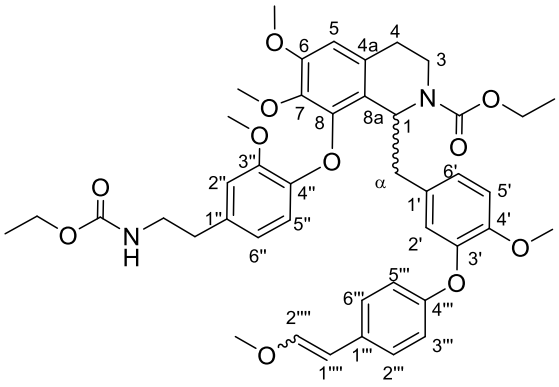
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.6 (C=O), 155.5 ('C=O), 154.8 (C-12), 154.4 (C-12'), 152.6 (C-6), 148.2 (C-6'), 145.8 (C-7'), 145.2 (C-8), 140.7 (C-7), 134.3 (C-10), 133.2 (C-9), 130.6 (C-14', C-10'), 130.3 (C-9'), 130.1 (C-4a), 129.5 (C-14), 129.2 (C-8a'), 128.4 (C-4a'), 123.5 (C-8a), 115.3 (C-13', C-11'), 114.4 (C-8'), 113.4 (C-5'), 112.5 (C-13), 111.7 (C-11), 109.8 (C-5), 61.2 ('O*C*H_2-CH_3, O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.7 (6-, 6'- or 12-OCH_3), 56.6 (6-, 6'- or 12-OCH_3), 56.6 (6-, 6'- or 12-OCH_3), 56.1 (C-1'), 52.1 (C-1), 42.2 (C-α'), 39.4 (C-α) 38.8 (C-3), 37.9 (C-3'), 28.3 (C-4'), 28.1 (C-4), 14.6 ('OCH_2-*C*H_3), 14.4 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2945, 2344, 1686, 1613, 1497, 1431, 1331, 1255, 1120, 1019, 949, 889, 743

Purity (HPLC, method a) = 67% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{47}{}^{79}BrN_2O_{10} + H]^+$ 819.2492, found: 819.2502

(±)-8-(4-(2-((Ethoxycarbonyl)amino)ethyl)-2-methoxyphenoxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(4'-methoxy-3'-(4-(2-methoxyvinyl)phenoxy)benzyl)-1,2,3,4-tetrahydroisoquinoline (69)



$C_{43}H_{50}N_2O_{11}$

M_W = 770.34 g/mol

Phenol **59** (100 mg, 0.157 mmol) and enol ether **60** (36.7 mg, 0.172 mmol) were coupled following General Procedure 3 (*inter*molecular Ullmann-type C–O coupling reaction). The reaction was completed after 5 days. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.26) gave **69** as a white solid.

yield: 74 mg, 0.096 mmol, 61%, white solid

mp: 59.5 – 61.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) *Z*-isomer: *δ* [ppm] = 7.45 – 7.38 (m, 1H, 2'''-H or 6'''-H), 7.11 – 7.05 (m, 1H, 2'''-H or 6'''-H), 6.86 (d, *J* = 12.9 Hz, 1H, 2''''-H), 6.81 (d, *J* = 8.3 Hz, 1H, 5'-H), 6.78 (d, *J* = 2.0 Hz, 1H, 6'-H), 6.77 – 6.71 (m, 3H, 2''-H, 3'''-H, 5'''-H), 6.67 (d, *J* = 1.9 Hz, 1H, 2'-H), 6.55 (dt, *J* = 8.3, 1.6 Hz, 1H, 6''-H), 6.50 (d, *J* = 8.2 Hz, 1H, 5''-H), 6.48 (s, 1H, 5-H), 5.80 (d, *J* = 12.8 Hz, 1H, 1''''-H), 5.32 (d, *J* = 8.7 Hz, 1H, 1-H), 4.58 (s, 1H, NH), 4.07 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH$_3$), 3.97 (d, *J* = 9.9 Hz, 1H, H-3), 3.91 – 3.75 (m, 2H, OC*H*$_2$-CH$_3$), 3.81 (s, 6H, 6-OCH$_3$, 3''-OCH$_3$), 3.72 (s, 3H, 4'-OCH$_3$), 3.64 (s, 3H, 2''''-OCH$_3$), 3.59 (s, 3H, 7-OCH$_3$), 3.35 (q, *J* = 6.9 Hz, 2H, NC*H*$_2$-CH$_2$), 3.32 – 3.24 (m, 1H, 3-H), 3.13 (dd, *J* = 14.1, 3.9 Hz, 1H, α-H), 2.85 – 2.73 (m, 2H, 4-H, α-H), 2.71 (t, *J* = 7.1 Hz, 2H, NCH$_2$-C*H*$_2$), 2.51 (d, *J* = 16.2 Hz, 1H, 4-H), 1.20 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.96 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) *Z*-isomer: *δ* [ppm] = 156.5 ('C=O), 156.4 (C-4'''), 152.6 (C-6), 150.4 (C-4'), 149.4 (C-3''), 148.1 (C-2''''), 146.6 (C-4''), 145.1 (C-3'), 140.7 (C-7), 133.2 (C-1''), 132.6 (C-1'), 130.4 (C-1'''), 130.2 (C-4a), 129.4 (C-2''' or C-6'''), 126.2 (C-2''' or C-6'''), 125.8 (C-6'), 124.1 (C-8a), 122.8 (C-2'), 120.8 (C-6''), 117.3 (C-3''' or C-5'''), 116.6 (C-3''' or C-5'''), 115.4 (C-5''), 114.3 (C-2''), 114.2 (C-5'), 109.7 (C-5), 105.4 (C-1''''), 61.0 (O*C*H$_2$-CH$_3$), 60.7 ('O*C*H$_2$-CH$_3$), 60.4 (7-OCH$_3$), 56.9 (2''''-OCH$_3$), 56.8 (4'-OCH$_3$), 56.6 (3''-OCH$_3$), 56.4 (6-OCH$_3$),

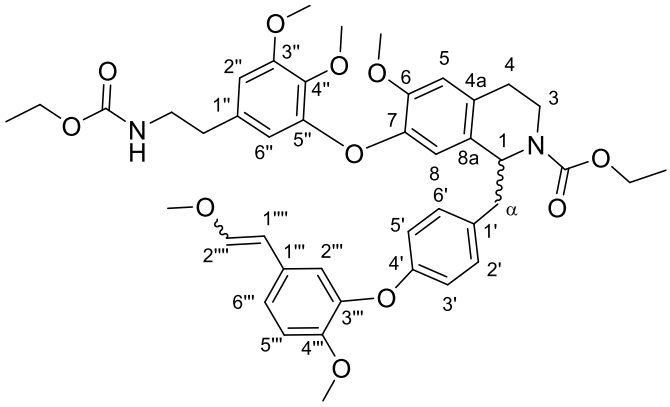
52.1 (C-1), 42.3 (N*C*H_2-CH_2), 39.6 (C-α), 37.7 (C-3), 35.9 (NCH_2-*C*H_2), 28.0 (C-4), 14.6 ('OCH_2-*C*H_3), 14.4 (OCH_2-*C*H_3). The resonances of C-8 and C=O could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2911, 1693, 1603, 1504, 1423, 1329, 1262, 1213, 1152, 1125, 1108, 1026, 839, 766

Purity (HPLC, method a) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{43}H_{50}N_2O_{11} + H]^+$ 771.3487, found: 771.3497

(±)-7-(5-(2-((Ethoxycarbonyl)amino)ethyl)-2,3-dimethoxyphenoxy)-*N*-ethoxycarbonyl-6-methoxy-1-(4'-(2-methoxy-5-(2-methoxyvinyl)phenoxy)benzyl)-1,2,3,4-tetrahydroisoquinoline (70)



$C_{43}H_{50}N_2O_{11}$

M_W = 770.34 g/mol

Phenol intermediate **66** (200 mg, 0.329 mmol) and enol ether **67** (87.9 mg, 0.361 mmol) were coupled following General Procedure 3 (*inter*molecular Ullmann-type C–O coupling reaction). The reaction was completed after 48 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.23) affording the product as a beige solid.

yield: 114 mg, 0.141 mmol, 43%, beige solid

mp: 47.0 – 50.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.95 – 6.84 (m, 4H, 5'''-H, 6'''-H, 2'-H, 6'-H), 6.81 – 6.74 (m, 4H, 2'''-H, 3'-H, 5'-H, 2''''-H), 6.68 (s, 1H, 5-H), 6.56 (s, 1H, 8-H), 6.46 (s, 1H, 2''-H), 6.21 (s, 1H, 6''-H), 5.71 (d, *J* = 12.8 Hz, 1H, 1''''-H), 5.14 (s, 1H, 1-H), 4.51 (s, 1H, NH), 4.04 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH$_3$), 4.04 – 3.90 (m, 3H, 3, OC*H*$_2$-CH$_3$), 3.84 (s, 3H, 3''-OCH$_3$), 3.80 (s, 3H, 4''-OCH$_3$), 3.78 (s, 3H, 6-OCH$_3$), 3.73 (s, 3H, 4'''-OCH$_3$), 3.60 (s, 3H, 2''''-OCH$_3$), 3.30 (q, *J* = 6.9 Hz, 2H, NC*H*$_2$-CH$_2$), 3.27 – 3.18 (m, 1H, 3-H), 2.95 (d, *J* = 6.6 Hz, 2H, α-H), 2.81 (ddd, *J* = 16.0, 9.5, 6.6 Hz, 1H, 4-H), 2.64 (t, *J* = 7.1 Hz, 2H, NCH$_2$-C*H*$_2$), 2.61 – 2.52 (m, 1H, H-4), 1.17 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 1.13 (t, *J* = 8.0 Hz, 3H, OCH$_2$-C*H*$_3$)

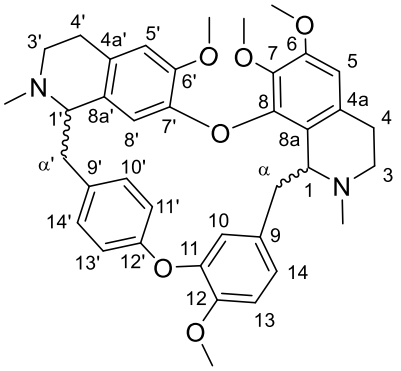
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 156.8 (C-4'), 156.4 ('C=O), 155.5 (C-3'''), 154.0 (C-3''), 151.1 (C-5''), 149.9 (C-4'''), 149.9 (C-6), 148.4 (C-2''''), 144.6 (C-7), 139.0 (C-4''), 134.2 (C-1''), 132.2 (C-1'), 130.6 (C-2', C-6'), 130.4 (C-4a), 130.0 (C-8a), 129.7 (C-1'''), 121.5 (C-6'''), 118.9 (C-8), 118.1 (C-2'''), 117.1 (C-3', C-5'), 114.8 (C-5'''), 114.1 (C-5), 111.6 (C-6''), 108.7 (C-2''), 105.0 (C-1''''), 61.2 (O*C*H$_2$-CH$_3$), 60.9 (4''-OCH$_3$), 60.7 ('O*C*H$_2$-CH$_3$), 56.8 (2''''-OCH$_3$), 56.7 (4''-OCH$_3$ or 3''-OCH$_3$), 56.7 (4''-OCH$_3$ or 3''-OCH$_3$), 56.6 (6-OCH$_3$), 55.8 (C-1), 42.2 (N*C*H$_2$-CH$_2$, C-α), 38.6 (C-3), 36.2 (NCH$_2$-*C*H$_2$), 28.4 (C-4), 14.6 (OCH$_2$-*C*H$_3$, 'OCH$_2$-*C*H$_3$). The resonance of C=O could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930, 2851, 1692, 1584, 1505, 1424, 1229, 1085, 1028, 941, 830, 767

Purity (HPLC, method a) = 85% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{43}H_{50}N_2O_{11} + K]^+$ 809.3052, found: 809.3045

(±)-Tetrandrine (*rac*-1) and (±)-isotetrandrine (*rac*-2)



$C_{38}H_{42}N_2O_6$

M_W = 622.30 g/mol

Carbamate **62** (45.0 mg, 0.0609 mmol of either (1*R*,1'*R*)/(1*S*,1'*S*) (**62a**) or (1*R*,1'*S*)/(1*S*,1'*R*) (**62b**) diastereomer) was reduced following General Procedure 4. The reaction was completed after 6 h. Purification was accomplished by flash column chromatography (dichloromethane → 1% triethylamine and 2% methanol in dichloromethane, R_f = 0.18). Racemic tetrandrine (*rac*-**1**) was obtained from **62a** as colourless needles (37.0 mg, 0.0594 mmol, 98%) and racemic isotetrandrine (*rac*-**2**) from **62b** as pale yellow prisms (37.3 mg, 0.0599 mmol, 98%), both after recrystallization from acetone. For the separation of the mixtures of diastereomers resulting from *intra*molecular *N*-acyl Pictet-Spengler reactions of **69** and **70** a preparative TLC method described by Lu *et al*.[132] was used with some modifications (0.5% triethylamine and 7.5% methanol in chloroform, R_f (*rac*-**1**) = 0.32; R_f (*rac*-**2**) = 0.22). Alternatively, preparative HPLC was performed on a Macherey-Nagel Nucleodur® 100-5 column (5 µm, 250 x 10 mm), eluent 1% methanol and 0.1% diethylamine in chloroform; flow rate 7.0 mL/min; temperature 25 °C; UV-detection at λ = 283 nm; (R_t (*rac*-**1**) = 4.11 min; R_t (*rac*-**2**) = 4.93 min).

(±)-Tetrandrine (*rac*-**1**):

yield: 37.0 mg, 0.0594 mmol, 98%, colourless needles

mp: 217.0 – 220.0 °C (lit.[154]: 252.0 – 253.0 °C (racemic tetrandrine (*rac*-**1**))

^{1}H NMR (500 MHz, $CDCl_3$) *δ* [ppm] = 7.34 (dd, *J* = 8.2, 2.2 Hz, 1H, 14'-H or 10'-H), 7.14 (dd, *J* = 8.2, 2.5 Hz, 1H, 13'-H or 11'-H), 6.88 (dd, *J* = 8.2, 1.6 Hz, 1H, 14-H), 6.86 (d, *J* = 8.1 Hz, 1H, 13-H), 6.80 (dd, *J* = 8.2, 2.6 Hz, 1H, 13'-H or 11'-H), 6.55 (d, *J* = 1.7 Hz, 1H, 10-H), 6.51 (s, 1H, 5'-H), 6.30 (s, 1H, 5-H), 6.30 (dd, *J* = 8.3, 2.2 Hz, 1H, 14'-H or 10'-H), 5.99 (s, 1H, 8'-H), 3.93 (s, 3H, 12-OCH_3), 3.87 (dd, *J* = 11.0, 5.6 Hz, 1H, 1'-H), 3.75 (s, 3H, 6-OCH_3), 3.73 (s, 1H, 1-H), 3.55 – 3.48 (m, 1H, 3-H), 3.43 (ddd, *J* = 12.6, 10.0, 5.9 Hz, 1H, 3'-H), 3.37 (s, 3H, 6'-OCH_3), 3.25 (dd, *J* = 12.5, 5.7 Hz, 1H, α'-H), 3.19 (s, 3H, 7-OCH_3), 2.99 – 2.89 (m, 3H, 3-H, 4-H, 4'-H), 2.89 – 2.84 (m, 1H, 3'-H), 2.80 (t, *J* = 11.7 Hz, 1H, α'-H), 2.75 – 2.72 (m, 1H, 4'-H),

2.70 (dd, *J* = 14.2, 10.2 Hz, 1H, α-H), 2.62 (s, 3H, 2'-NCH_3), 2.52 (d, *J* = 13.7 Hz, 1H, α-H), 2.45 – 2.39 (m, 1H, 4-H), 2.33 (s, 3H, 2-NCH_3)

^{13}C NMR (151 MHz, $CDCl_3$) *δ* [ppm] = 153.9 (C-12'), 151.5 (C-6), 149.5 (C-11), 148.7 (C-6'), 148.6 (C-8), 147.2 (C-12), 143.9 (C-7'), 138.0 (C-7), 135.4 (C-9'), 135.1 (C-9), 132.8 (C-14' or C-10'), 130.3 (C-14' or C-10'), 128.3 (C-4a), 128.2 (C-8a'), 128.1 (C-4a'), 123.1 (C-8a), 122.9 (C-14), 122.1 (C-13' or 11'), 122.0 (C-13' or 11'), 120.3 (C-8'), 116.4 (C-10), 112.9 (C-5'), 111.7 (C-13), 105.9 (C-5), 64.1 (C-1'), 61.6 (C-1), 60.4 (7-OCH_3), 56.3 (12-OCH_3), 56.0 (6'-OCH_3), 56.0 (6-OCH_3), 45.4 (C-3'), 44.3 (C-3), 42.8 (2'-NCH_3), 42.5 (2-NCH_3), 42.1 (C-α), 38.4 (C-α'), 25.4 (C-4'), 22.2 (C-4). The NMR data are identical with those of an authentic sample of tetrandrine.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2940, 2838, 1579, 1506, 1446, 1410, 1355, 1268, 1213, 1121, 1023, 844, 767, 744

Purity (HPLC, method c) = 98% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{42}N_2O_6 + H]^+$ 623.3116, found: 623.3111

(±)-Isotetrandrine (*rac*-**2**):

yield: 37.3 mg, 0.0599 mmol, 98%, pale yellow solid

mp: 175.5 – 182.0 °C (lit.[96]: 166.0 – 168.0 °C (enantiopure isotetrandrine (**2**)) A melting point of racemic isotetrandrine (*rac*-**2**) is not published yet).

^{1}H NMR (500 MHz, $CDCl_3$) *δ* [ppm] = 7.27 (dd, *J* = 8.4, 2.3 Hz, 1H, 14'-H or 10'-H), 7.10 (dd, *J* = 8.2, 2.5 Hz, 1H, 13'-H or 11'-H), 6.83 – 6.77 (m, 2H, 13-H, 14-H), 6.67 – 6.63 (m, 1H, 13'-H or 11'-H), 6.53 (s, 1H, 5'-H), 6.48 – 6.37 (m, 2H, 10-H, 14'-H or 10'-H), 6.27 (s, 1H, 5-H), 5.98 (s, 1H, 8'-H), 3.92 (s, 3H, 12-OCH_3), 3.88 – 3.81 (m, 2H, 1-H, 1'-H), 3.75 (s, 3H, 6-OCH_3), 3.61 (s, 3H, 6'-OCH_3), 3.44 – 3.36 (m, 1H, 3'-H), 3.33 – 3.21 (m, 2H, 3-H, α'-H), 3.13 (s, 3H, 7-OCH_3), 3.03 (d, *J* = 14.2 Hz, 1H, α-H), 2.96 – 2.86 (m, 3H, 4-H, 4'-H, α'-H), 2.85 – 2.76 (m, 3H, 3-H, 4'-H, 3'-H), 2.60 (d, *J* = 10.4 Hz, 1H, α-H), 2.57 (s, 3H, 2'-NCH_3), 2.45 – 2.31 (m, 1H, 4-H), 2.26 (s, 3H, 2-NCH_3)

^{13}C NMR (151 MHz, $CDCl_3$) *δ* [ppm] = 154.2 (12'), 152.0 (C-6), 150.0 (C-6'), 149.7 (C-11), 148.5 (C-4a), 147.1 (C-12), 143.8 (C-7'), 137.3 (C-7), 135.4 (C-9'), 132.2 (C-14' or C-10'), 130.3 (C-14' or 10'), 129.0 (C-4a'), 127.9 (C-8a'), 122.9 (C-14), 122.2 (C-13' or C-11'), 121.8 (C-13' or C-11'), 120.7 (C-8a), 120.0 (C-8'), 116.0 (C-9), 111.5 (C-13), 111.4 (C-5'), 105.7 (C-5), 64.0 (C-1'), 62.1 (C-1), 60.6 (7-O*C*H_3), 56.2 (12-OCH_3), 55.9 (6-O*C*H*3*), 55.7 (6'-OCH_3), 46.3 (C-3'), 43.0 (2'-NCH_3), 42.8 (2-NCH_3), 38.9 (C-α), 37.9 (C-α'), 25.9 (C-4'), 23.2 (C-4). The

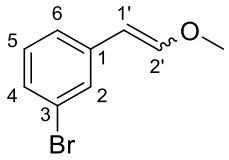
resonances of C-3 and C-8 could not be identified. The NMR data are in accordance with published data[140].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2933, 2834, 1582, 1506, 1445, 1413, 1260, 1229, 1114, 1030, 973, 865, 837, 772

Purity (HPLC, method c) = 97% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{42}N_2O_6 + H]^+$ 623.3116, found: 623.3108

(*E/Z*)-3-Bromo-1-(2-methoxyvinyl)benzene (71)



C_9H_9BrO

M_W = 211.98 g/mol

Prepared from 3-bromobenzaldehyde (1.00 g, 5.41 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, R_f = 0.25) to give the title compound as a colourless oil (*E,Z*-isomer ratio 0.92:1, estimated by NMR integrals). The compound is literature known[155-156].

yield: 940 mg, 4.41 mmol, 82%, colourless oil

NMR data of the major *Z*-isomer:

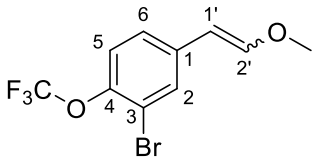
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.77 (t, J = 1.8 Hz, 1H, 2-H), 7.43 (dt, J = 7.8, 1.4 Hz, 1H, 6-H), 7.28 – 7.23 (m, 1H, 4-H), 7.16 – 7.09 (m, 1H, 5-H), 6.17 (d, J = 7.0 Hz, 1H, 2'-H), 5.15 (d, J = 7.0 Hz, 1H, 1'-H), 3.80 (s, 3H, 2'-OCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 149.2 (C-2'), 138.1 (C-1), 131.0 (C-2), 129.8 (C-5), 128.7 (C-4), 126.8 (C-6), 122.5 (C-3), 104.5 (C-1'), 61.1 (2'-OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3063, 2932, 2833, 1726, 1569, 1474, 1427, 1206, 1070, 782

HRMS (EI): *m/z* calcd for $[C_9H_9{}^{79}BrO]^{\bullet+}$ 211.9831, found: 211.9829

(*E/Z*)-3-Bromo-1-(2-methoxyvinyl)-4-(trifluoromethoxy)benzene (72)



$C_{10}H_8BrF_3O_2$

M_W = 295.97 g/mol

Prepared from 3-bromo-4-(trifluoromethoxy)benzaldehyde (300 mg, 1.12 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, R_f = 0.30) to give the title compound as a light yellow oil (*E,Z*-isomer ratio 1:0.71, estimated by NMR integrals).

yield: 266 mg, 0.895 mmol, 80%, light yellow oil

NMR data of the major *E*-isomer:

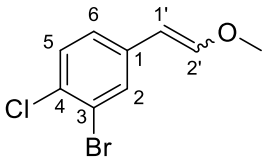
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.48 (d, *J* = 2.1 Hz, 1H, 2-H), 7.19 (dd, *J* = 8.4, 1.4 Hz, 1H, 5-H), 7.15 (dd, *J* = 8.5, 2.1 Hz, 1H, 6-H), 7.03 (d, *J* = 13.0 Hz, 1H, 2'-H), 5.71 (d, *J* = 12.9 Hz, 1H, 1'-H), 3.70 (s, 3H, 2'-OCH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 150.6 (C-2'), 144.2 (d, *J* = 2.0 Hz, C-4), 137.2 (C-1), 130.1 (C-2), 125.1 (C-6), 122.6 (C-5), 120.7 (q, *J* = 258.7 Hz, O*C*F_3), 116.5 (C-3), 102.9 (C-1'), 56.9 (2'-OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2940, 2838, 1641, 1492, 1247, 1156, 1096, 932, 833

HRMS (EI): *m/z* calcd for $[C_{10}H_8{}^{79}BrF_3O_2]^{\bullet+}$ 295.9654, found: 295.9651

(*E/Z*)-3-Bromo-4-chloro-1-(2-methoxyvinyl)benzene (73)



C_9H_8BrClO

M_W = 245.95 g/mol

Prepared from 3-bromo-4-chlorobenzaldehyde (500 mg, 2.28 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, R_f = 0.36) to give the title compound as a light yellow oil (*E,Z*-isomer ratio 1.08:1, estimated by NMR integrals).

yield: 490 mg, 1.98 mmol, 87%, light yellow oil

NMR data of the major *E*-isomer:

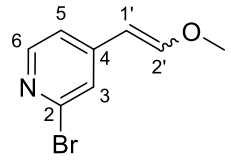
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.47 (d, *J* = 2.1 Hz, 1H, 2-H), 7.30 (d, *J* = 7.2 Hz, 1H, 5-H), 7.08 (dd, *J* = 8.3, 2.1 Hz, 1H, 6-H), 7.03 (d, *J* = 13.0 Hz, 1H, 2'-H), 5.69 (d, *J* = 13.0 Hz, 1H, 1'-H), 3.69 (s, 3H, OCH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 150.3 (C-2'), 137.0 (C-1), 131.0 (C-4), 130.4 (C-5), 130.1 (C-2), 125.1 (C-6), 122.7 (C-3) 103.1 (C-1'), 56.9 (OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2934, 2833, 1701, 1640, 1467, 1192, 1120, 1023, 822

HRMS (EI): *m/z* calcd for $[C_9H_8{}^{79}Br{}^{35}ClO]^{\bullet+}$ 245.9442, found: 245.9444

(*E/Z*)-2-Bromo-4-(2-methoxyvinyl)pyridine (75)



C_8H_8BrNO

M_W = 212.98 g/mol

Prepared from 2-bromoisonicotinaldehyde (**74**, 300 mg, 1.61 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (20% ethyl acetate in hexanes, R_f = 0.32) to give the title compound as a light yellow oil (*E,Z*-isomer ratio 1:0.79, estimated by NMR integrals).

yield: 290 mg, 1.35 mmol, 84%, yellow oil

NMR data of the major *E*-isomer:

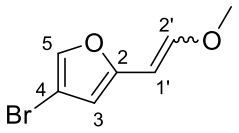
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.16 (d, *J*=5.3, 1H, 6-H), 7.28 – 7.28 (m, 1H, 3-H), 7.26 (d, *J*=13.0, 1H, 2'-H), 7.04 (ddd, *J*=5.3, 1.6, 0.5, 1H, 5-H), 5.63 (d, *J*=13.0, 1H, 1'-H), 3.73 (s, 3H, OCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 153.5 (C-2'), 150.0 (C-6), 147.6 (C-4), 142.9 (C-2), 123.6 (C-3), 118.8 (C-5), 101.9 (C-1'), 57.2 (OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2937, 2082, 1635, 1522, 1378, 1278, 1076, 984, 936, 846, 716

HRMS (EI): *m/z* calcd for $[C_8H_8{}^{79}BrNO]^{\bullet+}$ 212.9784, found: 212.9785

(*E/Z*)-4-Bromo-2-(2-methoxyvinyl)furan (76)



$C_7H_7BrO_2$

M_W = 201.96 g/mol

Prepared from 4-bromo-2-furaldehyde (300 mg, 1.71 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, R_f = 0.19) to give the title compound as a light yellow oil (*E,Z*-isomer ratio 1:0.81, estimated by NMR integrals).

yield: 280 mg, 1.38 mmol, 81%, light yellow oil

NMR data of the major *E*-isomer:

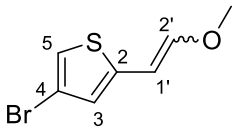
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.23 (d, *J*=0.8, 1H, 5-H), 7.07 (d, *J*=12.9, 1H, 2'-H), 6.06 – 6.05 (m, 1H, 3-H), 5.58 (d, *J*=12.8, 1H, 1'-H), 3.66 (s, 3H, OCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 152.9 (C-2), 150.2 (C-2'), 138.4 (C-5), 107.2 (C-3), 101.0 (C-4), 94.7 (C-1'), 56.8 (OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 1780, 1645, 1453, 1362, 1212, 1118, 1019, 922, 790

HRMS (EI): *m/z* calcd for $[C_7H_7{}^{79}BrO_2]^{\bullet+}$ 201.9624, found: 201.9621

(*E/Z*)-4-Bromo-2-(2-methoxyvinyl)thiophene (77)



C_7H_7BrOS

M_W = 217.94 g/mol

Prepared from 4-bromothiophene-2-carboxaldehyde (0.500 g, 2.62 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (hexanes, R_f = 0.28) to give the title compound as a light yellow oil (*E,Z*-isomer ratio 1:1.13, estimated by NMR integrals).

yield: 471 mg, 2.15 mmol, 82%, light yellow oil

NMR data of the *E*-isomer:

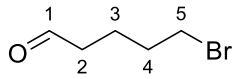
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.97 (d, J = 12.9 Hz, 1H, 2'-H), 6.89 (d, J = 1.4 Hz, 1H, 5-H), 6.70 – 6.68 (m, 1H, 3-H), 5.87 (d, J = 12.8 Hz, 1H, 1'-H), 3.67 (s, 3H, OCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 149.9 (C-2'), 141.4 (C-2), 125.0 (C-3), 118.5 (C-5), 109.8 (C-4), 98.6 (C-1'), 57.0 (OCH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3110, 2933, 2849, 2053, 1727, 1637, 1221, 1093, 819, 722

HRMS (EI): *m/z* calcd for $[C_7H_7{}^{79}BrOS]^{\bullet+}$ 217.9395, found: 217.9395

5-Bromo-1-pentanal (79)



C_5H_9BrO

M_W = 163.98 g/mol

Pyridinium chlorochromate (503 mg, 2.33 mmol, 1.3 eq.) was suspended in 10 mL anhydrous dichloromethane under nitrogen atmosphere. Then 5-bromo-1-pentanol (**78**, 300 mg, 1.80 mmol) was added and the mixture was stirred for 6 h at ambient temperature. The volatiles were removed *in vacuo* and purification of the residue by flash column chromatography (25% diethyl ether in hexanes, R_f = 0.43) gave the product as a colourless oil. The ^{1}H NMR data is in good agreement with literature[157].

yield: 191 mg, 1.16 mmol, 64%, colourless oil

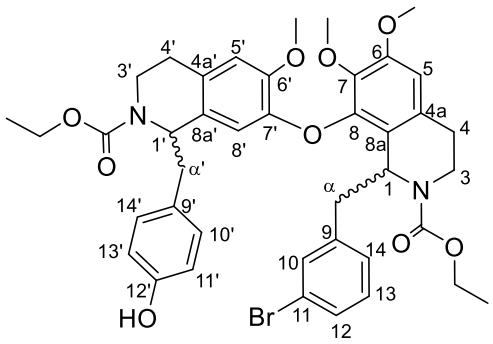
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.78 (t, J = 1.5 Hz, 1H, 1-H), 3.42 (t, J = 6.5 Hz, 2H, 5-H), 2.49 (td, J = 7.1, 1.5 Hz, 2H, 2-H), 1.95 – 1.86 (m, 2H, 4-H), 1.84 – 1.75 (m, 2H, 3-H)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 201.7 (C-1), 42.9 (C-2), 33.0 (C-5), 31.9 (C-4), 20.6 (C-3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954, 2865, 2840, 1725, 1437, 1358, 1122, 1058

HRMS (EI): *m/z* calcd for $[C_5H_9{}^{79}BrO]^{\bullet+}$ 162.9753, found: 162.9752

(±)-8-((1-(4-Hydroxybenzyl)-*N*-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline (**80**; separable mixture of racemic diastereomers)



$C_{41}H_{45}BrN_2O_9$

M_W = 788.23 g/mol

Carbamate **66** (250 mg, 0.411 mmol) and enol ether **71** (160 mg, 0.751 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TfOH as catalyst. The reaction was completed after 4 h. Purification by flash column chromatography (20% ethyl acetate in dichloromethane, R_f = 0.13 (1*R*,1'*R*)/(1*S*,1'*S*) isomers and 0.23 (1*R*,1'*S*)/(1*S*,1'*R*) isomers) gave the title compounds as white solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 111 mg, 0.141 mmol, 34%, white solid

mp: 112.0 – 113.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.30 – 7.22 (m, 1H, 12-H), 7.18 (t, *J* = 1.8 Hz, 1H, 10-H), 7.03 (t, *J* = 7.7 Hz, 1H, 13-H), 6.95 (d, *J* = 7.6 Hz, 1H, 14-H), 6.81 – 6.76 (m, 2H, 10'-H, 14'-H), 6.70 (s, 1H, 5'-H), 6.58 – 6.51 (m, 3H, 5-H, 11'-H, 13'-H), 6.20 (s, 1H, 8'-H), 5.34 (d, *J* = 9.6 Hz, 1H, 1-H), 5.02 (t, *J* = 6.5 Hz, 1H, 1'-H), 4.68 (s, 1H, OH), 4.16 – 4.05 (m, 1H, 3-H), 4.00 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH$_3$), 3.96 – 3.85 (m, 1H, 3'-H), 3.90 (s, 3H, 6'-OCH$_3$), 3.85 (s, 3H, 6-OCH$_3$), 3.88 – 3.70 (m, 2H, OC*H*$_2$-CH$_3$), 3.63 (s, 3H, 7-OCH$_3$), 3.33 (ddd, *J* = 13.2, 10.4, 5.0 Hz, 1H, 3-H), 3.18 (ddd, *J* = 13.3, 9.5, 4.4 Hz, 1H, 3'-H), 3.10 (dd, *J* = 13.9, 3.6 Hz, 1H, α-H), 2.93 – 2.85 (m, 1H, 4-H), 2.84 (t, *J* = 6.8 Hz, 2H, α'-H), 2.81 – 2.72 (m, 2H, α-H, 4'-H), 2.60 (d, *J* = 16.4 Hz, 1H, 4-H), 2.54 (dt, *J* = 16.0, 4.6 Hz, 1H, 4'-H), 1.14 (t, *J* = 7.0 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.90 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 ('C=O), 155.3 (C=O), 154.2 (C-12'), 152.7 (C-6), 148.2 (C-6'), 145.9 (C-7'), 141.6 (C-9), 140.9 (C-7), 132.5 (C-10), 130.5 (C-10', C-14'), 130.5 (C-9'), 130.0 (C-8a'), 129.4 (C-13), 129.2 (C-12), 128.5 (C-4a'), 128.2 (C-14), 123.8 (C-8a), 122.1 (C-11), 115.4 (C-11', C-13'), 114.1 (C-8'), 113.4 (C-5'), 110.1 (C-5), 61.2 ('O*C*H$_2$-

CH_3), 61.1 (OCH_2-CH_3), 60.7 (7-OCH_3), 56.7 (6'-OCH_3 or 6-OCH_3), 56.6 (6'-OCH_3 or 6-OCH_3), 55.9 (C-1'), 51.9 (C-1), 42.1 (C-α'), 40.1 (C-α), 38.8 (C-3'), 37.4 (C-3), 28.3 (C-4'), 27.9 (C-4), 14.6 ('OCH_2-CH_3), 14.2 (OCH_2-CH_3). The resonances of C-8 and C-4a could not be identified

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930, 1693, 1513, 1426, 1332, 1199, 1112, 1021, 835, 765

Purity (HPLC, method e) = 90% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{45}{}^{79}BrN_2O_9 + H]^+$ 789.2381, found: 789.2383

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 95.0 mg, 0.121 mmol, 29%, white solid

mp: 99.0 – 101.5 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) δ [ppm] = 7.28 (dt, *J* = 7.8, 1.6 Hz, 1H, 12-H), 7.24 (s, 1H, 10-H), 7.05 (t, *J* = 7.7 Hz, 1H, 13-H), 6.99 (d, *J* = 7.6 Hz, 1H, 14-H), 6.81 – 6.74 (m, 2H, 10'-H, 14'-H), 6.70 (s, 1H, 5'-H), 6.60 – 6.53 (m, 2H, 11'-H, 13'-H), 6.52 (s, 1H, 5-H), 6.11 (s, 1H, 8'-H), 5.32 (s, 1H, 1-H), 5.18 (s, 1H, OH), 4.99 (t, *J* = 6.5 Hz, 1H, 1'-H), 4.15 – 4.06 (m, 1H, 3-H), 4.01 (q, *J* = 7.3 Hz, 2H, 'OC*H*$_2$-CH_3), 3.96 – 3.87 (m, 1H, 3'-H), 3.89 (s, 3H, 6'-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.86 – 3.76 (m, 2H, OC*H*$_2$-CH_3), 3.60 (s, 3H, 7-OCH_3), 3.36 (ddd, *J* = 13.1, 10.0, 4.8 Hz, 1H, 3-H), 3.23 (dd, *J* = 14.0, 4.1 Hz, 2H, α-H, 3'-H), 2.97 – 2.83 (m, 3H, α-H, α'-H, 4-H), 2.82 – 2.72 (m, 2H, α'-H, 4'-H), 2.57 (dt, *J* = 16.0, 4.5 Hz, 2H, 4'-H, 4-H), 1.15 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.96 (s, 3H, OCH_2-C*H*$_3$)

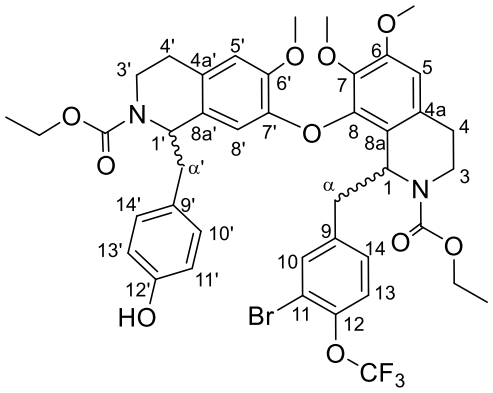
^{13}C NMR (101 MHz, TCl_2, 100 °C) δ [ppm] = 155.5 (C=O, 'C=O), 154.4 (C-12'), 152.6 (C-6), 148.2 (C-6'), 145.7 (C-7'), 141.6 (C-9), 140.7 (C-7), 132.6 (C-10), 130.5 (C-10', C-14'), 130.3 (C-9'), 129.4 (C-13), 129.2 (C-12), 129.2 (C-8a'), 128.4 (C-4a'), 128.3 (C-14), 123.4 (C-8a), 122.1 (C-11), 115.3 (C-11', C-13'), 114.3 (C-8'), 113.3 (C-5'), 109.8 (C-5), 61.2 (O*C*H_2-CH_3, 'O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.6 (6'-OCH_3, 6-OCH_3), 56.1 (C-1'), 52.0 (C-1), 42.2 (C-α'), 40.2 (C-α), 38.8 (C-3'), 37.8 (C-3), 28.3 (C-4'), 28.1 (C-4), 14.6 ('OCH_2-*C*H_3), 14.3 (OCH_2-*C*H_3). The resonances of C-8 and C-4a could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2935, 1689, 1512, 1426, 1332, 1239, 1112, 1023, 769

Purity (HPLC, method e) = 92% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{45}{}^{79}BrN_2O_9 + H]^+$ 789.2381, found: 789.2390

(±)-8-((1-(4-Hydroxybenzyl)-*N*-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-bromo-4'-trifluoromethoxy-benzyl)-1,2,3,4-tetrahydroisoquinoline (**81**; separable mixture of racemic diastereomers)



$C_{42}H_{44}BrF_3N_2O_{10}$

M_W = 872.21 g/mol

Carbamate **66** (250 mg, 0.411 mmol) and enol ether **72** (146 mg, 0.493 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TfOH as catalyst. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.10 (1*R*,1'*R*)/(1*S*,1'*S*) isomers and 0.15 (1*R*,1'*S*)/(1*S*,1'*R*) isomers) gave the title compounds as white solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 134 mg, 0.153 mmol, 37%, white solid

mp: 91.5 – 92.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.31 (d, *J* = 2.0 Hz, 1H, 10-H), 7.10 (dd, *J* = 8.4, 1.6 Hz, 1H, 13-H), 6.99 (dd, *J* = 8.4, 2.1 Hz, 1H, 14-H), 6.81 – 6.76 (m, 2H, 10'-H, 14'-H), 6.70 (s, 1H, 5'-H), 6.57 – 6.51 (m, 2H, 11'-H, 13'-H), 6.54 (s, 1H, 5-H), 6.19 (s, 1H, 8'-H), 5.29 (s, 1H, 1-H), 5.02 (t, *J* = 6.5 Hz, 1H, 1'-H), 4.64 (s, 1H, OH), 4.15 – 4.03 (m, 1H, 3-H), 4.00 (q, *J* = 7.0 Hz, 2H, 'OC*H*$_2$-CH$_3$), 3.90 (s, 3H, 6'-OCH$_3$), 3.85 (s, 3H, 6-OCH$_3$), 3.97 – 3.71 (m, 3H, OC*H*$_2$-CH$_3$, 3'-H), 3.62 (s, 3H, 7-OCH$_3$), 3.39 – 3.29 (m, 1H, 3-H), 3.24 – 3.13 (m, 1H, 3'-H), 3.11 (dd, *J* = 13.9, 3.7 Hz, 1H, α-H), 2.91 – 2.72 (m, 5H, α-H, α'-H, 4'-H, 4-H), 2.62 (d, *J* = 15.4 Hz, 1H, 4-H), 2.54 (dt, *J* = 16.0, 4.6 Hz, 1H, 4'-H), 1.14 (t, *J* = 6.9 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.88 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.4 ('C=O), 155.2 (C=O), 154.2 (C-12'), 152.8 (C-6), 148.1 (C-6'), 145.8 (C-7'), 145.0 (C-12), 140.9 (C-7), 139.9 (C-9), 134.8 (C-10), 130.5 (C-10', C-14'), 130.4 (C-9'), 129.6 (C-14), 129.3 (C-8a'), 123.5 (C-8a), 121.5 (C-13), 115.6 (C-11), 115.4 (C-11', C-13'), 114.1 (C-8'), 113.4 (C-5'), 110.2 (C-5), 61.2 ('O*C*H$_2$-CH$_3$), 61.1 (O*C*H$_2$-CH$_3$), 60.7 (7-OCH$_3$), 56.7, 56.6 (6'-OCH$_3$, 6-OCH$_3$), 55.9 (C-1'), 51.9 (C-1), 42.1 (C-

α'), 39.6 (C-α), 38.8 (C-3'), 38.2 (C-3), 28.3 (C-4'), 27.9 (C-4), 14.6 ('OCH_2-*C*H_3), 14.1 (OCH_2-*C*H_3).The resonances of C-8, C-4a, C-4a' and OCF_3 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 1668, 1612, 1514, 1426, 1332, 1247, 1168, 1119, 1023, 763

Purity (HPLC, method b) = 85% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{44}{}^{79}BrF_3N_2O_{10} + H]^+$ 873.2204, found: 873.2217

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 91 mg, 0.104 mmol, 25%, white solid

mp: 93.5 – 95.0 °C

^{1}H NMR (400 MHz, TcI_2, 100 °C) δ [ppm] = 7.37 (d, *J* = 2.0 Hz, 1H, 10-H), 7.12 (dd, *J* = 8.4, 1.6 Hz, 1H, 13-H), 7.03 (dd, *J* = 8.4, 2.1 Hz, 1H, 14-H), 6.81 – 6.72 (m, 2H, 10'-H, 14'-H), 6.70 (s, 1H, 5'-H), 6.59 – 6.53 (m, 2H, 11'-H, 13'-H), 6.52 (s, 1H, 5-H), 6.09 (s, 1H, 8'-H), 5.29 (d, *J* = 5.6 Hz, 1H, 1-H), 4.98 (t, *J* = 6.4 Hz, 1H, 1'-H), 4.10 – 4.01 (m, 1H, 3-H), 4.02 (q, *J* = 7.2 Hz, 2H, 'OC*H*$_2$-CH_3), 3.88 (s, 3H, 6'-OCH_3), 3.96 – 3.76 (m, 3H, OC*H*$_2$-CH_3, 3'-H), 3.83 (s, 3H, 6-OCH_3), 3.58 (s, 3H, 7-OCH_3), 3.37 (ddd, *J* = 13.3, 10.0, 4.8 Hz, 1H, 3-H), 3.23 (dd, *J* = 13.8, 4.0 Hz, 2H, α-H, 3'-H), 2.95 – 2.81 (m, 3H, α-H, α'-H, 4-H), 2.81 – 2.72 (m, 2H, α'-H, 4'-H), 2.64 – 2.54 (m, 2H, 4'-H, 4-H), 1.16 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.96 (br s, 3H, OCH_2-C*H*$_3$)

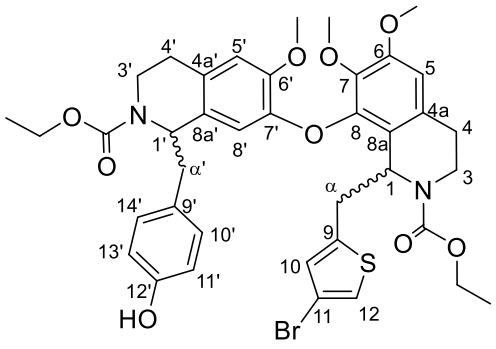
^{13}C NMR (101 MHz, TcI_2, 100 °C) δ [ppm] = 155.5 (C=O, 'C=O), 154.3 (C-12'), 154.2 (C-6), 148.2 (C-6'), 145.6 (C-7'), 145.2 (C-12), 143.1 (C-7), 139.9 (C-9), 135.0 (C-10), 130.6 (C-10', C-14'), 130.4 (C-9'), 130.0 (C-8a'), 129.7 (C-14), 123.0 (C-8a), 121.9 (C-13), 115.3 (C-11), 115.3 (C-11', C-13'), 114.4 (C-8'), 113.3 (C-5'), 109.8 (C-5), 61.3 ('O*C*H_2-CH_3), 61.2 (O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.6, 56.5 (6'-OCH_3, 6-OCH_3), 56.5 (C-1'), 52.0 (C-1), 42.2 (C-α'), 39.7 (C-α), 38.9 (C-3'), 38.0 (C-3), 28.3 (C-4'), 28.1 (C-4), 14.6 ('OCH_2-*C*H_3), 14.3 (OCH_2-*C*H_3). The resonances of C-8, C-4a, C-4a' and OCF_3 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2922, 1668, 1613, 1514, 1455, 1333, 1253, 1170, 1120, 1024, 764

Purity (HPLC, method b) = 90% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{44}{}^{79}BrF_3N_2O_{10} + H]^+$ 873.2204, found: 873.2217

(±)-8-((1-(4-Hydroxybenzyl)-*N*-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-((4'-bromothiophen-2'-yl)methyl)-1,2,3,4-tetrahydroisoquinoline (**83**; separable mixture of racemic diastereomers)



$C_{39}H_{43}BrN_2O_9S$

M_W = 794.19 g/mol

Carbamate **66** (300 mg, 0.493 mmol) and enol ether **77** (130 mg, 0.591 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TfOH as catalyst. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.10 (1*R*,1'*R*)/(1*S*,1'*S*) isomers and 0.15 (1*R*,1'*S*)/(1*S*,1'*R*) isomers) gave the title compounds as white solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 137 mg, 0.172 mmol, 35%, white solid

mp: 108.5 – 114.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.96 (d, *J* = 1.4 Hz, 1H, 12-H), 6.81 – 6.77 (m, 2H, 14'-H and 10'-H), 6.68 (s, 1H, 5'-H), 6.58 (s, 1H, 10-H), 6.57 – 6.54 (m, 2H, 13'-H and 11'-H), 6.52 (s, 1H, 5-H), 6.22 (s, 1H, 8'-H), 5.33 (d, *J* = 9.5 Hz, 1H, 1-H), 5.02 (t, *J* = 6.4 Hz, 1H, 1'-H), 4.58 (s, 1H, OH), 4.11 – 4.05 (m, 1H, 3-H), 4.01 (q, *J* = 7.0 Hz, 2H, 'OC*H*$_2$-CH$_3$), 3.94 – 3.81 (m, 3H, 3'-H, OC*H*$_2$-CH$_3$), 3.87 (s, 3H, 6'-OCH$_3$), 3.85 (s, 3H, 6-OCH$_3$), 3.61 (s, 3H, 7-OCH$_3$), 3.31 (dd, *J* = 15.2, 3.7 Hz, 1H, α-H), 3.29 – 3.12 (m, 2H, 3-H, 3'-H), 3.01 (dd, *J* = 15.1, 9.3 Hz, 1H, α-H), 2.84 (dd, *J* = 9.1, 6.5 Hz, 1H, α'-H), 2.91 – 2.72 (m, 3H, 4-H, 4'-H, α'-H), 2.56 (ddd, *J* = 20.0, 11.4, 3.9 Hz, 2H, 4-H, 4'-H), 1.14 (t, *J* = 7.0 Hz, 3H, 'OCH$_2$-C*H*$_3$), 1.01 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (C=O or C=O'), 155.4 (C=O or C=O'), 154.2 (C-12'), 152.8 (C-6), 148.4 (C-6'), 146.0 (C-7'), 142.6 (C-9), 140.8 (C-7), 130.6 (C-14' and C-10'), 130.4 (C-9'), 129.3 (C-8a'), 128.6 (C-10), 123.1 (C-8a), 121.3 (C-12), 115.4 (C-13' and C-11'), 114.4 (C-8'), 113.5 (C-5'), 110.0 (C-5), 108.9 (C-11), 61.3 (O*C*H$_2$-CH$_3$), 61.2 ('O*C*H$_2$-CH$_3$), 60.7 (7-OCH$_3$), 56.6 (6-O*C*H$_3$ or 6'-OCH$_3$), 56.5 (6-OCH$_3$ or 6'-OCH$_3$), 55.9 (C-1'), 51.9 (C-1),

42.1 (C-α'), 38.7 (C-3'), 37.6 (C-3), 34.6 (C-α), 28.3 (C-4'), 27.9 (C-4), 14.6 ('OCH_2-CH_3), 14.3 (OCH_2-CH_3). The resonances of C-8, C-4a and C-4a' could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2843, 1667, 1513, 1422, 1331, 1222, 1109, 1023, 821, 764

Purity (HPLC, method c) = 93% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{39}H_{43}{}^{79}BrN_2O_9S - H]^-$ 793.1800, found: 793.1829

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 130 mg, 0.163 mmol, 33%, white solid

mp: 110.0 – 119.5 °C

^{1}H NMR (400 MHz, TcI_2, 100 °C) δ [ppm] = 6.98 (d, *J* = 1.4 Hz, 1H, 12-H), 6.80 – 6.76 (m, 2H, 14'-H, 10'-H), 6.68 (s, 1H, 5'-H), 6.62 (s, 1H, 10-H), 6.59 – 6.54 (m, 2H, 13'-H and 11'-H), 6.50 (s, 1H, 5-H), 6.11 (s, 1H, 8'-H), 5.29 (d, *J* = 7.0 Hz, 1H, 1-H), 4.99 (t, *J* = 6.6 Hz, 1H, 1'-H), 4.02 (q, *J* = 7.2 Hz, 3H, 3'-H, 'OC*H*$_2$-CH_3), 4.00 – 3.88 (m, 3H, 3-H, OC*H*$_2$-CH_3), 3.86 (s, 3H, 6'-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.58 (s, 3H, 7-OCH_3), 3.45 (dd, *J* = 15.2, 3.9 Hz, 1H, α-H), 3.35 – 3.20 (m, 2H, 3-H, 3'-H), 3.08 (dd, *J* = 15.1, 8.9 Hz, 1H, α-H), 2.93 – 2.81 (m, 2H, 4'-H, α'-H), 2.77 (dd, *J* = 13.9, 7.0 Hz, 2H, 4-H, α'-H), 2.63 – 2.51 (m, 2H, 4-H, 4'-H), 1.16 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 1.07 (br s, 3H, OCH$_2$-C*H*$_3$)

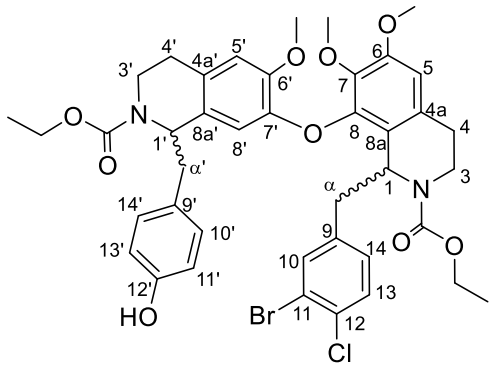
^{13}C NMR (101 MHz, TcI_2, 100 °C) δ [ppm] = 155.7 (C=O or C=O'), 155.5 (C=O or C=O'), 154.3 (C-12'), 152.8 (C-6), 148.3 (C-6'), 145.7 (C-7'), 142.6 (C-9), 140.7 (C-7), 130.6 (C-14' and C-10'), 130.4 (C-9'), 129.2 (C-8a'), 128.7 (C-10), 122.6 (C-8a), 121.3 (C-12), 115.3 (C-13' and C-11'), 114.6 (C-8'), 113.4 (C-5'), 109.7 (C-5), 108.9 (C-11), 61.4 (O*C*H$_2$-CH_3), 61.2 ('O*C*H$_2$-CH_3), 60.7 (7-OCH_3), 56.5 (6-OCH_3 and 6'-OCH_3), 56.1 (C-1'), 52.0 (C-1), 42.2 (C-α'), 38.9 (C-3), 38.0 (C-3'), 34.6 (C-α), 28.3 (C-4'), 28.0 (C-4), 14.6 ('OCH_2-CH_3), 14.5 (OCH_2-CH_3). The resonances of C-8, C-4a and C-4a' could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2936, 1690, 1511, 1421, 1221, 1099, 1022, 819,764

Purity (HPLC, method c) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{39}H_{43}{}^{79}BrN_2O_9S - H]^-$ 793.1800, found: 793.1829

(±)-8-((1-(4-Hydroxybenzyl)-*N*-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(3'-bromo-4'-chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (**84**; separable mixture of racemic diastereomers)



$C_{41}H_{44}BrClN_2O_9$

M_W = 822.19 g/mol

Carbamate **66** (350 mg, 0.575 mmol) and enol ether **73** (171 mg, 0.695 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TfOH as catalyst. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.09 (1*R*,1'*R*)/(1*S*,1'*S*) isomers and 0.13 (1*R*,1'*S*)/(1*S*,1'*R*) isomers) gave the title compounds as a white solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 128 mg, 0.155 mmol, 27%, white solid

mp: 84.0 – 88.0 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) δ [ppm] = 7.28 (d, *J* = 2.0 Hz, 1H, 10-H), 7.24 (d, *J* = 8.2 Hz, 1H, 13-H), 6.91 (dd, *J* = 8.1, 2.0 Hz, 1H, 14-H), 6.81 – 6.76 (m, 2H, 14'-H and 10'-H), 6.70 (s, 1H, 5'-H), 6.57 – 6.52 (m, 2H, 13'-H and 11'-H), 6.54 (s, 1H, 5-H), 6.19 (s, 1H, 8'-H), 5.34 – 5.27 (m, 1H, 1-H), 5.02 (t, *J* = 6.3 Hz, 1H, 1'-H), 4.66 (s, 1H, OH), 4.15 – 4.04 (m, 1H, 3-H), 4.00 (q, *J* = 6.9 Hz, 2H, 'OC*H*$_2$-CH$_3$), 3.89 (s, 3H, 6'-OCH$_3$), 3.85 (s, 3H, 6-OCH$_3$), 3.93 – 3.74 (m, 3H, OC*H*$_2$-CH$_3$, 3'-H), 3.62 (s, 3H, 7-OCH$_3$), 3.37 – 3.26 (m, 1H, 3-H), 3.24 – 3.13 (m, 2H, 3'-H), 3.07 (dd, *J* = 14.0, 3.8 Hz, 1H, α-H), 2.92 – 2.73 (m, 5H, 4-H, α-H, 4'-H, α'-H), 2.61 (d, *J* = 14.5 Hz, 1H, 4-H), 2.54 (dt, *J* = 16.1, 4.5 Hz, 1H, 4'-H), 1.14 (t, *J* = 7.0 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.90 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, TCl_2, 100 °C) δ [ppm] = 155.4 (C=O or C=O'), 155.3 (C=O or C=O'), 154.2 (C-12'), 152.7 (C-6), 148.2 (C-6'), 145.8 (C-7'), 140.9 (C-7), 139.7 (C-9), 134.6 (C-10), 132.1 (C-12), 130.5 (C-14' and C-10'), 130.5 (C-9'), 129.7 (C-13 or C-14), 129.6 (C-13 or C-14), 129.2 (C-8a'), 128.6 (C-4a'), 123.5 (C-8a), 121.8 (C-11), 115.4 (C-13' and C-11'), 114.1 (C-8'), 113.4 (C-5'), 110.1 (C-5), 61.2 (O*C*H$_2$-CH$_3$ and 'O*C*H$_2$-CH$_3$), 60.7 (7-OCH$_3$), 56.7 (6-OCH$_3$), 56.6 (6'-OCH$_3$), 55.9 (C-1'), 51.9 (C-1), 42.1 (C-α'), 39.6 (C-α), 38.8 (C-3'), 37.5 (C-3), 28.3 (C-4'), 27.9

(C-4), 14.6 ('OCH_2-CH_3), 14.2 (OCH_2-CH_3). The resonances of C-8 and C-4a could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3174, 1689, 1509, 1419, 1201, 1097, 1021, 762

Purity (HPLC, method c) = 89% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{44}{}^{79}Br^{35}ClN_2O_9 - H]^-$ 821.1846, found: 821.1851

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 122 mg, 0.150 mmol, 26%, white solid

mp: 106.5 – 108.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.34 (d, *J* = 2.0 Hz, 1H, 10-H), 7.25 (d, *J* = 8.1 Hz, 1H, 13-H), 6.95 (dd, *J* = 8.2, 2.0 Hz, 1H, 14-H), 6.80 – 6.75 (m, 2H, 14'-H and 10'-H), 6.69 (s, 1H, 5'-H), 6.58 – 6.53 (m, 2H, 13'-H and 11'-H), 6.51 (s, 1H, 5-H), 6.08 (s, 1H, 8'-H), 5.28 (d, *J* = 8.5 Hz, 1H, 1-H), 4.98 (t, *J* = 6.7 Hz, 1H, 1'-H), 4.02 (q, *J* = 6.9 Hz, 3H, 3'-H, 'OCH_2-CH_3), 3.88 (s, 3H, 6'-OCH_3), 3.87 (ddd, *J* = 25.0, 16.3, 5.2 Hz, 3H, 3-H, OCH_2-CH_3), 3.83 (s, 3H, 6-OCH_3), 3.58 (s, 3H, 7-OCH_3), 3.36 (ddd, *J* = 13.2, 9.9, 4.7 Hz, 1H, 3'-H), 3.28 – 3.22 (m, 1H, 3-H), 3.20 (dd, *J* = 13.8, 4.1 Hz, 1H, α-H), 2.93 – 2.83 (m, 3H, α-H, 4'-H, α'-H), 2.82 – 2.73 (m, 2H, 4-H, α'-H), 2.63 – 2.54 (m, 2H, 4-H, 4'-H), 1.15 (t, *J* = 7.1 Hz, 3H, 'OCH_2-CH_3), 0.99 (br s, 3H, OCH_2-CH_3)

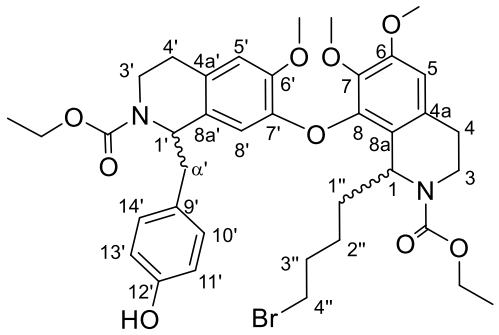
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (C=O), 155.5 (C=O'), 154.4 (C-12'), 152.7 (C-6), 148.2 (C-6'), 145.6 (C-7'), 140.7 (C-7), 139.7 (C-9), 134.7 (C-10), 132.1 (C-12), 130.6 (C-14' and C-10'), 130.4 (C-9'), 129.7 (C-14), 129.7 (C-13), 129.2 (C-8a'), 128.5 (C-4a'), 123.1 (C-8a), 121.8 (C-11), 115.3 (C-13' and C-11'), 114.4 (C-8'), 113.3 (C-5'), 109.8 (C-5), 61.3 (OCH_2-CH_3), 61.2 ('OCH_2-CH_3), 60.7 (7-OCH_3), 56.6 (6-OCH_3 and 6'-OCH_3), 56.1 (C-1'), 52.0 (C-1), 42.2 (C-α'), 39.8 (C-α), 38.8 (C-3), 38.0 (C-3'), 28.3 (C-4'), 28.1 (C-4), 14.6 ('OCH_2-CH_3), 14.3 (OCH_2-CH_3). The resonances of C-8 and C-4a could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3355, 2841, 1689, 1668, 1514, 1424, 1331, 1203, 1110, 1023, 765

Purity (HPLC, method c) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{44}{}^{79}Br^{35}ClN_2O_9 - H]^-$ 821.1846, found: 821.1852

(±)-8-((1-(4-Hydroxybenzyl)-*N*-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxycarbonyl-6,7-dimethoxy-1-(4-bromobutyl)-1,2,3,4-tetrahydroisoquinoline (**85**; separable mixture of racemic diastereomers)



$C_{38}H_{47}BrN_2O_9$

M_W = 754.25 g/mol

Carbamate **66** (300 mg, 0.493 mmol) and aldehyde **79** (98 mg, 0.591 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TfOH as catalyst. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.10 (precursor of **RMS10**) and 0.16 (precursor of **RMS9**) gave the title compounds as a white solids.

Precursor of **RMS10**:

yield: 133 mg, 0.178 mmol, 36%, white solid

mp: 77.5 – 78.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.80 – 6.75 (m, 2H, 14'-H and 10'-H), 6.65 (s, 1H, 5'-H), 6.62 – 6.58 (m, 2H, 13'-H and 11'-H), 6.52 (s, 1H, 5-H), 6.19 (s, 1H, 8'-H), 5.12 (s, 1H, 1-H), 5.02 (t, *J* = 6.5 Hz, 1H, 1'-H), 4.14 – 3.94 (m, 6H, 3-H, 3'-H, 'OC*H*$_2$-CH$_3$, OC*H*$_2$-CH$_3$), 3.86 (s, 3H, 6'-OCH$_3$), 3.82 (s, 3H, 6-OCH$_3$), 3.58 (s, 3H, 7-OCH$_3$), 3.27 (t, *J* = 6.9 Hz, 2H, 4''-H), 3.26 – 3.20 (m, 1H, 3-H), 3.16 (ddd, *J* = 13.5, 9.7, 4.4 Hz, 1H, 3'-H), 2.93 – 2.84 (m, 1H, 4-H), 2.82 (t, *J* = 5.5 Hz, 1H, α'-H), 2.78 – 2.72 (m, 1H, 4'-H), 2.68 (dt, *J* = 16.5, 4.5 Hz, 1H, 4-H), 2.51 (dt, *J* = 16.0, 4.6 Hz, 1H, 4'-H), 1.86 – 1.68 (m, 3H, 1''-H, 3''-H), 1.68 – 1.56 (m, 1H, 1''-H), 1.47 – 1.38 (m, 2H, 2''-H), 1.13 (t, *J* = 7.0 Hz, 6H, 'OCH$_2$-C*H*$_3$ and OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.7 ('C=O), 155.4 (C=O), 154.5 (C-12'), 152.4 (C-6), 148.2 (C-6'), 146.3 (C-7'), 145.1 (C-8), 140.6 (C-7), 130.4 (C-14' and C-10'), 130.1 (C-9'), 129.6 (C-8a'), 129.3 (C-4a), 128.3 (C-4a'), 125.1 (C-8a), 115.4 (C-13' and C-11'), 114.2 (C-8'), 113.6 (C-5'), 110.2 (C-5), 61.2 ('O*C*H$_2$-CH$_3$ or O*C*H$_2$-CH$_3$), 61.1 ('O*C*H$_2$-CH$_3$ or O*C*H$_2$-CH$_3$), 60.6 (7-OCH$_3$), 56.7 (6-OCH$_3$ or 6'-OCH$_3$), 56.6 (6-OCH$_3$ or 6'-OCH$_3$), 55.8 (C-1'), 50.1 (C-1),

42.1 (C-α'), 38.6 (C-3'), 37.4 (C-3), 33.7 (C-1''), 33.6 (C-4''), 32.3 (C-3''), 28.2 (C-4'), 27.8 (C-4), 24.9 (C-2''), 14.6 ('OCH_2-*C*H_3), 14.5 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2928, 2854, 2605, 2498, 1692, 1513, 1426, 1331, 1234, 1100, 1026, 767

Purity (HPLC, method c) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{47}{}^{79}BrN_2O_9 + H]^+$ 755.2538, found: 755.2548

Precursor of **RMS9**:

yield: 85.5 mg, 0.113 mmol, 23%, white solid

mp: 200.5 °C

^{1}H NMR (400 MHz, TcI_2, 100 °C) δ [ppm] = 6.81 – 6.75 (m, 2H, 14'-H and 10'-H), 6.66 (s, 1H, 5'-H), 6.60 – 6.55 (m, 2H, 13'-H and 11'-H), 6.49 (s, 1H, 5-H), 6.10 (s, 1H, 8'-H), 5.15 – 5.07 (m, 1H, 1-H), 4.97 (t, *J* = 6.6 Hz, 1H, 1'-H), 4.16 – 3.97 (m, 6H, 3-H, 3'-H, 'OC*H*$_2$-CH_3, OC*H*$_2$-CH_3), 3.85 (s, 3H, 6'-OCH_3), 3.81 (s, 3H, 6-OCH_3), 3.56 (s, 3H, 7-OCH_3), 3.33 (t, *J* = 6.9 Hz, 2H, 4''-H), 3.30 – 3.20 (m, 2H, 3-H, 3'-H), 2.96 – 2.85 (m, 2H, 4-H, α'-H), 2.84 – 2.74 (m, 2H, 4'-H, α'-H), 2.69 (dt, *J* = 16.2, 4.4 Hz, 1H, 4-H), 2.57 (dt, *J* = 15.5, 4.4 Hz, 1H, 4'-H), 1.91 – 1.78 (m, 3H, 1''-H, 3''-H), 1.73 – 1.61 (m, 1H, 1''-H), 1.51 – 1.40 (m, 2H, 2''-H), 1.21 – 1.12 (m, 6H, 'OCH$_2$-C*H*$_3$ and OCH$_2$-C*H*$_3$)

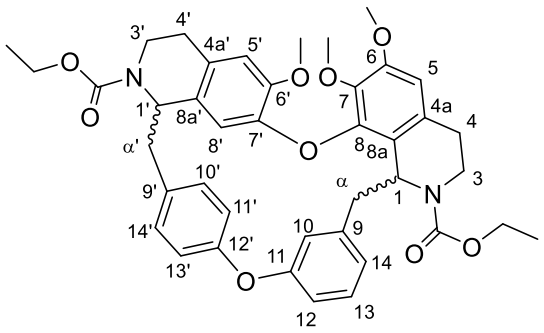
^{13}C NMR (101 MHz, TcI_2, 100 °C) δ [ppm] = 155.9 (C=O or C=O'), 155.5 (C=O or C=O'), 154.4 (C-12'), 152.4 (C-6), 148.4 (C-6'), 146.1 (C-7'), 145.3 (C-8), 140.5 (C-7), 130.6 (C-14' and C-10'), 130.4 (C-9'), 129.6 (C-8a'), 124.7 (C-8a), 115.3 (C-13' and C-11'), 114.7 (C-8'), 113.5 (C-5'), 109.8 (C-5), 61.3 ('O*C*H$_2$-CH_3 or O*C*H$_2$-CH_3), 61.2 ('O*C*H$_2$-CH_3 or O*C*H$_2$-CH_3), 60.6 (7-OCH_3), 56.7 (6-OCH_3 or 6'-OCH_3), 56.5 (6-OCH_3 or 6'-OCH_3), 56.1 (C-1'), 50.3 (C-1), 42.2 (C-α'), 38.9 (C-3'), 37.8 (C-3), 33.9 (C-1''), 33.6 (C-4''), 32.5 (C-3''), 28.3 (C-4'), 28.1 (C-4), 25.0 (C-2''), 14.6 ('OCH_2-*C*H_3 and OCH_2-*C*H_3). The resonances of C-4a and C-4a' could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2851, 1690, 1611, 1513, 1427, 1332, 1233, 1100, 1023, 806, 761

Purity (HPLC, method c) = 93% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{47}{}^{79}BrN_2O_9 + H]^+$ 755.2538, found: 755.2558

(±)-*N*,*N'*-Bis-(ethoxycarbonyl)-12-desmethoxy-bisnortetrandrine and –isotetrandrine (**86**)



$C_{41}H_{44}N_2O_9$

M_W = 708.31 g/mol

Previously separated diastereomers of bisbenzylisoquinoline **80** (50.0 mg, 0.0633 mmol of each diastereomer) were reacted following General Procedure 3 (*intra*molecular Ullmann coupling). The reactions were completed after 42 h. Purification was accomplished by flash column chromatography (30% acetone in hexanes, R_f = 0.18) and the products obtained as beige solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 34.6 mg, 0.0488 mmol, 77%, beige solid

mp: 83.0 – 83.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.39 (d, *J* = 8.4 Hz, 1H, 10'-H or 14'-H), 7.14 (t, *J* = 7.8 Hz, 1H, 13-H), 7.10 (dd, *J* = 8.1, 2.5 Hz, 1H, 11'-H or 13'-H), 6.97 (dd, *J* = 8.1, 2.5 Hz, 1H, 12-H), 6.64 (s, 1H, 5'-H), 6.70 – 6.60 (m, 2H, 11'-H or 13'-H, 14-H), 6.48 (t, *J* = 1.9 Hz, 1H, 10-H), 6.33 (s, 1H, 5-H), 6.22 – 6.16 (m, 1H, 10'-H or 14'-H), 6.18 (s, 1H, 8'-H), 5.31 (dd, *J* = 8.1, 3.6 Hz, 1H, 1-H), 5.05 (d, *J* = 10.4 Hz, 1H, 1'-H), 4.36 – 4.21 (m, 3H, 'OC*H*$_2$-CH$_3$, 3-H), 3.99 (ddd, *J* = 12.2, 5.7, 3.5 Hz, 1H, 3'-H), 3.86 – 3.76 (m, 2H, OC*H*$_2$-CH$_3$), 3.74 (s, 3H, 6-OCH$_3$), 3.49 (dd, *J* = 13.5, 5.0 Hz, 1H, α'-H), 3.41 (td, *J* = 11.7, 4.8 Hz, 2H, 3'-H, 3-H), 3.34 (s, 3H, 6'-OCH$_3$), 3.26 (s, 3H, 7-OCH$_3$), 3.19 – 3.08 (m, 1H, 4'-H), 2.95 – 2.80 (m, 2H, 4'-H, 4-H), 2.80 – 2.72 (m, 2H, α-H), 2.71 – 2.59 (m, 2H, α'-H, 4-H), 1.36 (t, *J* = 6.8 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.89 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 160.3 (C-11), 155.9 (C=O or 'C=O), 155.6 (C=O or 'C=O), 154.2 (C-12'), 152.1 (C-6), 149.1 (C-6'), 147.0 (C-8), 144.9 (C-7'), 142.0 (C-9), 138.9 (C-7), 134.6 (C-9'), 132.2 (C-10' or C-14'), 130.1 (C-10' or C-14'), 129.1 (C-13), 128.8 (C-8a'), 128.2 (C-4a'), 122.9 (C-8a), 122.2 (C-14), 122.0 (C-11' or C-13'), 121.6 (C-11' or C-13'), 119.7 (C-8'), 115.4 (C-10, C-12), 114.0 (C-5'), 107.3 (C-5), 61.4 ('O*C*H$_2$-CH$_3$), 60.7 (O*C*H$_2$-CH$_3$), 60.3

(7-OCH_3), 57.7 (C-1'), 57.0 (6'-OCH_3), 56.3 (6-OCH_3), 53.5 (C-1), 42.0 (C-α'), 3', 41.6 (C-α), 36.6 (C-3), 28.0 (C-4), 27.9 (C-4'), 14.8 (OCH_2-*C*H_3, 'OCH_2-*C*H_3). The resonance of C-4a could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2854, 1691, 1586, 1506, 1417, 1332, 1278, 1211, 1107, 1025, 839, 765

Purity (HPLC, method e) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{44}N_2O_9 + H]^+$ 709.3120, found: 709.3125

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 18 mg, 0.0254 mmol, 40%, beige solid

mp: 92.0 – 93.5 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) *δ* [ppm] = 7.36 (d, *J* = 8.2 Hz, 1H, 10'-H or 14'-H), 7.11 (t, *J* = 7.8 Hz, 1H, 13-H), 7.05 (d, *J* = 7.2 Hz, 1H, 11'-H or 13'-H), 6.94 (dd, *J* = 8.2, 2.5 Hz, 1H, 12-H), 6.64 (s, 1H, 5'-H), 6.66 – 6.60 (m, 2H, 11'-H or 13'-H, 14-H), 6.40 – 6.32 (m, 2H, 10-H, 10'-H or 14'-H), 6.28 (s, 1H, 5-H), 6.20 (s, 1H, 8'-H), 5.29 (d, *J* = 9.4 Hz, 1H, 1-H), 5.11 (dd, *J* = 9.8, 6.5 Hz, 1H, 1'-H), 4.29 – 4.15 (m, 3H, 'OC*H*$_2$-CH_3, 3-H), 3.97 – 3.89 (m, 1H, 3'-H), 3.88 – 3.76 (m, 2H, OC*H*$_2$-CH_3), 3.73 (s, 3H, 6-OCH_3), 3.60 (s, 3H, 6'-OCH_3), 3.57 – 3.51 (m, 1H, α'-H), 3.49 – 3.41 (m, 1H, 3'-H), 3.37 – 3.27 (m, 1H, 3-H), 3.21 – 3.14 (m, 2H, α-H, 4'-H), 3.16 (s, 3H, 7-OC*H*$_3$), 2.88 – 2.76 (m, 2H, 4'-H, 4-H), 2.71 (dd, *J* = 12.8, 10.5 Hz, 1H, α'-H), 2.62 (dd, *J* = 13.7, 9.6 Hz, 1H, α-H), 2.53 – 2.42 (m, 1H, 4-H), 1.33 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.96 (br s, 3H, OCH_2-C*H*$_3$)

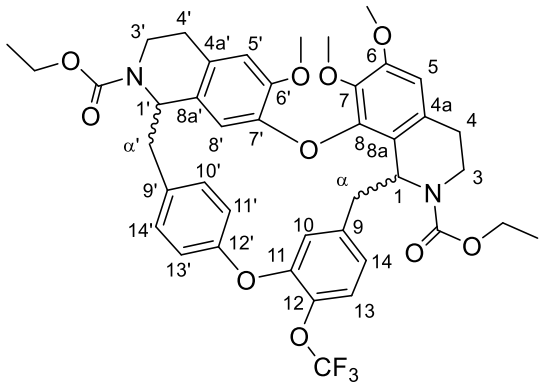
^{13}C NMR (101 MHz, TCl_2, 100 °C) *δ* [ppm] = 160.4 (C-11), 155.8, 155.4 ('C=O, C=O), 154.3 (C-12'), 152.5 (C-6), 150.1 (C-6'), 144.4 (C-7'), 142.4 (C-9), 137.9 (C-7), 134.7 (C-9'), 131.5 (C-10' or C-14'), 130.5 (C-4a'), 130.0 (C-10' or C-14'), 128.9 (C-13), 128.3 (C-8a'), 122.4 (C-14), 122.0 (C-11', C-13'), 120.6 (C-8a), 119.6 (C-8'), 115.8 (C-10), 115.4 (C-12), 111.8 (C-5'), 106.8 (C-5), 61.3 ('O*C*H_2-CH_3), 60.9 (O*C*H_2-CH_3), 60.5 (7-OCH_3), 57.0 (C-1'), 56.3 (6-OCH_3), 56.1 (6'-OCH_3), 54.2 (C-1), 41.8 (C-α'), 41.5 (C-3'), 39.6 (C-α), 36.8 (C-3), 28.2 (C-4), 28.1 (C-4'), 14.8 ('OCH_2-*C*H_3), 14.2 (OCH_2-*C*H_3). The resonances of C-4a and C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1693, 1584, 1507, 1418, 1330, 1276, 1208, 1099, 1022, 837, 769

Purity (HPLC, method e) = 88% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{44}N_2O_9 + H]^+$ 709.3120, found: 709.3121

(±)-*N*,*N'*-Bis-(ethoxycarbonyl)-12-desmethoxy-12-trifluoromethoxy-bisnortetrandrine and –isotetrandrine (**87**)



$C_{42}H_{43}F_3N_2O_{10}$

M_W = 792.29 g/mol

Previously separated diastereomers of bisbenzylisoquinoline **81** (60.0 mg, 0.0687 mmol of each diastereomer) were reacted following General Procedure 3 (*intra*molecular Ullmann coupling). The reactions were completed after 30 h. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.23) and the products obtained as beige solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 35.0 mg, 0.0441 mmol, 64%, beige solid

mp: 77.5 – 78.5 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) δ [ppm] = 7.41 (d, *J* = 8.4 Hz, 1H, 10'-H or 14'-H), 7.15 – 7.07 (m, 2H, 13-H and 11'-H or 13'-H), 6.68 – 6.64 (m, 1H, 11'-H or 13'-H), 6.65 (s, 1H, 5'-H), 6.62 (dd, *J* = 8.1, 2.0 Hz, 1H, 14-H), 6.59 (d, *J* = 1.9 Hz, 1H, 10-H), 6.33 (s, 1H, 5-H), 6.22 (dd, *J* = 8.3, 2.2 Hz, 1H, 10'-H or 14'-H), 6.17 (s, 1H, 8'-H), 5.29 (dd, *J* = 7.9, 2.8 Hz, 1H, 1-H), 5.05 (s, 1H, 1'-H), 4.37 – 4.27 (m, 1H, 3-H), 4.26 (q, *J* = 7.2 Hz, 2H, 'OC*H*$_2$-CH$_3$), 4.00 (ddd, *J* = 12.2, 5.7, 3.5 Hz, 1H, 3'-H), 3.87 – 3.76 (m, 2H, OC*H*$_2$-CH$_3$), 3.74 (s, 3H, 6-OCH$_3$), 3.51 (d, *J* = 8.5 Hz, 1H, α'-H), 3.41 (td, *J* = 11.8, 4.9 Hz, 2H, 3'-H, 3-H), 3.34 (s, 3H, 6'-OCH$_3$), 3.26 (s, 3H, 7-OCH$_3$), 3.15 (td, *J* = 11.3, 10.8, 5.6 Hz, 1H, 4'-H), 2.94 – 2.84 (m, 1H, 4-H), 2.84 – 2.72 (m, 3H, α-H, 4'-H), 2.73 – 2.61 (m, 2H, α'-H, 4-H), 1.36 (t, *J* = 6.2 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.87 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, TCl_2, 100 °C) δ [ppm] = 155.9 ('C=O), 155.5 (C=O), 153.5 (C-12'), 152.3 (C-6), 152.2 (C-11), 149.1 (C-6'), 147.0 (C-8), 144.8 (C-7'), 140.8 (C-9), 138.9 (C-7), 136.6 (q, *J* = 1.8 Hz, C-12), 135.3 (C-9'), 132.3, 130.3 (C-10', C-14'), 130.2 (C-4a'), 128.7 (C-8a'), 122.5 (C-13), 122.5 (C-8a), 122.0 (C-14), 121.9, 121.3 (C-11', C-13'), 119.6 (C-8'), 117.4 (C-10), 113.9 (C-5'), 107.4 (C-5), 61.4 ('O*C*H$_2$-CH$_3$), 60.8 (O*C*H$_2$-CH$_3$), 60.3 (7-OCH$_3$), 57.6 (C-1'), 56.9 (6'-OCH$_3$), 56.3 (6-OCH$_3$), 53.4 (C-1), 42.0 (C-α', C-3'), 41.1 (C-α), 36.6 (C-3), 27.9 (C-4), 27.8

(C-4'), 14.8 ('OCH_2-CH_3), 14.0 (OCH_2-CH_3). The resonances of C-4a and OCF_3 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1693, 1505, 1423, 1281, 1248, 1201, 1110, 1024, 842, 767

Purity (HPLC, method b) = 96% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{43}F_3N_2O_{10} + H]^+$ 793.2943, found: 793.2955

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 15.0 mg, 0.0189 mmol, 28%, beige solid

mp: 73.5 – 74.5 °C

^{1}H NMR (400 MHz, TCl_2, 100 °C) δ [ppm] = 7.38 (d, *J* = 8.0 Hz, 1H, 10'-H or 14'-H), 7.11 – 7.05 (m, 2H, 11'-H or 13'-H, 13-H), 6.64 (s, 1H, 5'-H), 6.62 (dt, *J* = 8.3, 2.6 Hz, 2H, 11'-H or 13'-H, 14-H), 6.47 (s, 1H, 10-H), 6.39 (d, *J* = 8.4 Hz, 1H, 10'-H or 14'-H), 6.29 (s, 1H, 5-H), 6.19 (s, 1H, 8'-H), 5.26 (d, *J* = 9.4 Hz, 1H, 1-H), 5.12 (q, *J* = 7.5 Hz, 1H, 1'-H), 4.29 – 4.15 (m, 3H, 'OC*H*$_2$-CH_3, 3-H), 3.99 – 3.88 (m, 1H, 3'-H), 3.88 – 3.76 (m, 2H, OC*H*$_2$-CH_3), 3.73 (s, 3H, 6-OCH_3), 3.60 (s, 3H, 6'-OCH_3), 3.58 – 3.52 (m, 1H, α'-H), 3.45 (td, *J* = 11.5, 4.9 Hz, 1H, 3'-H), 3.35 – 3.25 (m, 1H, 3-H), 3.22 – 3.10 (m, 2H, α-H, 4'-H), 3.16 (s, 3H, 7-OCH_3), 2.86 – 2.73 (m, 2H, 4'-H, 4-H), 2.72 (dd, *J* = 12.8, 10.6 Hz, 1H, α'-H), 2.61 (dd, *J* = 13.8, 9.7 Hz, 1H, α-H), 2.50 (d, *J* = 16.3 Hz, 1H, 4-H), 1.34 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.98 (br s, 3H, OCH_2-C*H*$_3$)

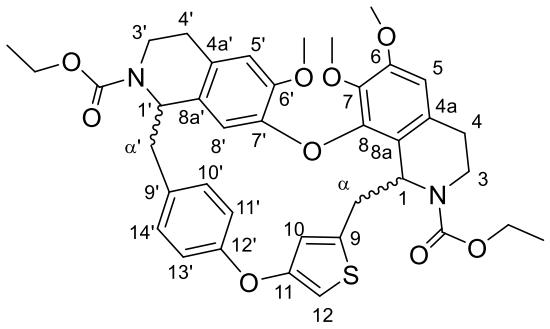
^{13}C NMR (101 MHz, TCl_2, 100 °C) δ [ppm] = 155.8, 155.3 ('C=O, C=O), 153.8 (C-12'), 152.6 (C-6), 152.3 (C-11), 150.1 (C-6'), 144.3 (C-7'), 141.1 (C-9), 138.0 (C-7), 136.7 (C-12), 135.4 (C-9'), 131.7, 130.7 (C-10', C-14'), 128.2 (C-8a'), 122.2 (C-11' or C-13' or C-13, C-14), 121.7 (C-11' or C-13' or C-13), 120.5 (C-8a), 119.6 (C-8'), 117.9 (C-10), 111.8 (C-5'), 106.9 (C-5), 61.4 ('O*C*H_2-CH_3), 61.0 (O*C*H_2-CH_3), 60.5 (7-OCH_3), 56.9 (C-1'), 56.3 (6-OCH_3), 56.0 (6'-OCH_3), 54.1 (C-1), 41.8 (C-α', C-3'), 39.3 (C-α), 36.9 (C-3), 28.2 (C-4), 28.1 (C-4'), 14.8 ('OCH_2-*C*H_3), 14.2 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1694, 1506, 1420, 1273, 1248, 1200, 1099, 1021, 841, 770

Purity (HPLC, method e) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{43}F_3N_2O_{10} + H]^+$ 793.2943, found: 793.2955

(±)-*N*,*N'*-Bis-(ethoxycarbonyl) ring C-thiophene analogues of bisnortetrandrine and –isotetrandrine (**89**)



$C_{39}H_{42}N_2O_9S$

M_W = 714.26 g/mol

Previously separated diastereomers of bisbenzylisoquinoline **83** (100 mg, 0.126 mmol of each diastereomer) were reacted following General Procedure 3 (*intra*molecular Ullmann coupling). The reactions were completed after 70 h. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.17) and the products obtained as white solids.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 51.3 mg, 0.0718 mmol, 57%, white solid

mp: 74.5 – 76.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.35 (d, *J* = 8.2 Hz, 1H, 14'-H or 10'-H), 7.13 (dd, *J* = 8.2, 2.5 Hz, 1H, 13'-H or 11'-H), 6.70 (d, *J* = 5.8 Hz, 1H, 13'-H or 11'-H), 6.60 (s, 1H, 5'-H), 6.41 (d, *J* = 1.7 Hz, 1H, 12-H), 6.34 (s, 1H, 5-H), 6.28 (s, 1H, 10-H), 6.19 (dd, *J* = 8.3, 2.2 Hz, 1H, 14'-H or 10'-H), 6.01 (s, 1H, 8'-H), 5.45 (d, *J* = 6.8 Hz, 1H, 1-H), 5.00 (s, 1H, 1'-H), 4.30 – 4.19 (m, 2H, 'OCH_2-CH_3), 4.11 – 4.02 (m, 1H, 3-H), 4.01 – 3.88 (m, 3H, 3'-H, OCH_2-CH_3), 3.73 (s, 3H, 6-OCH_3), 3.50 – 3.37 (m, 3H, 3-H, 3'-H, α'-H), 3.32 (s, 3H, 6'-OCH_3), 3.22 (s, 3H, 7-OCH_3), 3.15 – 3.04 (m, 1H, 4'-H), 3.00 (dd, *J* = 15.2, 2.6 Hz, 1H, α-H), 2.91 – 2.75 (m, 3H, 4-H, α-H, 4'-H), 2.69 (dt, *J* = 16.1, 4.9 Hz, 1H, 4-H), 2.63 (d, *J* = 11.8 Hz, 1H, α'-H), 1.35 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-CH_3), 1.06 (br s, 3H, OCH$_2$-CH_3)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 157.0 (C-12'), 152.3 (C-6), 149.3 (C-6'), 144.9 (C-7'), 141.5 (C-9), 139.2 (C-7), 134.4 (C-9'), 132.1 (C-14' or C-10'), 130.3 (C-4a'), 129.8 (C-14' or C-10'), 128.6 (C-8a'), 123.5 (C-8a), 121.0 (C-13' and C-11'), 120.2 (C-8'), 118.2 (C-10), 113.7 (C-5'), 107.3 (C-5), 101.1 (C-12), 61.4 ('O*C*H$_2$-CH$_3$), 61.1 (O*C*H$_2$-CH$_3$), 60.2 (7-OCH_3), 57.7 (C-1'), 56.6 (6'-OCH_3), 56.3 (6-OCH_3), 54.2 (C-1), 41.6 (C-3' and C-α'), 38.5 (C-α), 38.2 (C-3), 28.0 (C-4), 27.9 (C-4'), 14.8 ('OCH$_2$-*C*H$_3$), 14.4 (OCH$_2$-*C*H$_3$). The resonances of 'C=O, C=O, C-8, C-4a and C-11 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2929, 1693, 1558, 1505, 1416, 1277, 1219, 1101, 1020, 875, 770

Purity (HPLC, method c) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{39}H_{42}N_2O_9S + H]^+$ 715.2684, found: 715.2686

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 15.3 mg, 0.0214 mmol, 17%, white solid

mp: 116.0 – 119.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.31 (dd, *J* = 8.2, 2.2 Hz, 1H, 14'-H or 10'-H), 7.08 (dd, *J* = 7.9, 2.2 Hz, 1H, 13'-H or 11'-H), 6.66 (dd, *J* = 8.3, 2.6 Hz, 1H, 13'-H or 11'-H), 6.62 (s, 1H, 5'-H), 6.40 (dd, *J* = 8.2, 2.2 Hz, 1H, 14'-H or 10'-H), 6.31 (d, *J* = 1.7 Hz, 1H, 10-H), 6.27 (s, 1H, 5-H), 6.17 (s, 1H, 8'-H), 5.97 (d, *J* = 1.7 Hz, 1H, 12-H), 5.32 (d, *J* = 8.0 Hz, 1H, 1-H), 5.11 (t, *J* = 8.7 Hz, 1H, 1'-H), 4.29 – 4.19 (m, 3H, 3-H, 'OC*H*$_2$-CH$_3$), 4.00 – 3.88 (m, 3H, 3'-H, OC*H*$_2$-CH$_3$), 3.72 (s, 3H, 6-OCH$_3$), 3.58 (d, *J* = 6.6 Hz, 1H, α'-H), 3.55 (s, 3H, 6'-OCH$_3$), 3.40 (td, *J* = 11.4, 4.9 Hz, 1H, 3'-H), 3.32 (d, *J* = 15.0 Hz, 1H, α-H), 3.27 – 3.13 (m, 2H, 3-H, 4'-H), 3.12 (s, 3H, 7-OCH$_3$), 2.86 – 2.70 (m, 3H, 4-H, 4'-H, α'-H), 2.68 – 2.54 (m, 2H, 4-H, α-H), 1.33 (t, *J* = 7.0 Hz, 3H, 'OCH$_2$-C*H*$_3$), 1.09 (br s, 3H, OCH$_2$-C*H*$_3$)

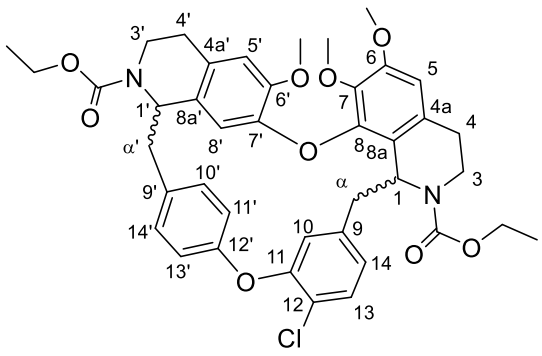
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 156.8 (C-12'), 155.8 (C=O), 152.6 (C-6), 150.1 (C-6'), 144.0 (C-7'), 141.8 (C-9), 137.8 (C-7), 134.8 (C-9'), 131.6 (C-14' or C-10'), 129.6 (C-14' or C-10'), 128.3 (C-8a'), 122.1 (C-13' or C-11'), 121.3 (C-13' or C-11'), 120.3 (C-8a), 119.8 (C-8'), 118.0 (C-12), 111.8 (C-5'), 106.7 (C-5), 99.6 (C-10), 61.3 ('O*C*H$_2$-CH$_3$), 61.2 (O*C*H$_2$-CH$_3$), 60.5 (7-OCH$_3$), 57.1 (C-1'), 56.3 (6-OCH$_3$), 56.0 (6'-OCH$_3$), 55.7 (C-1), 41.9 (C-3'), 41.2 (C-α'), 37.2 (C-3), 35.6 (C-α), 28.1 (C-4), 28.0 (C-4'), 14.8 ('OCH$_2$-*C*H$_3$), 14.6 (OCH$_2$-*C*H$_3$). The resonances of 'C=O, C-4a', C-4a, C-8, and C-11 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2854, 1694, 1557, 1505, 1417, 1219, 1098, 1022, 842, 770

Purity (HPLC, method c) = 90% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{39}H_{42}N_2O_9S + H]^+$ 715.2684, found: 715.2688

(±)-*N*,*N'*-Bis-(ethoxycarbonyl)-12-desmethoxy-12-chloro-bisnortetrandrine and –isotetrandrine (**90**)



$C_{41}H_{43}ClN_2O_9$

M_W = 742.27 g/mol

Previously separated diastereomers of bisbenzylisoquinoline **84** (110 mg, 0.133 mmol of each diastereomer) were reacted following General Procedure 3 (*intra*molecular Ullmann coupling). The reactions were completed after 60 h. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.15) and the products obtained as a white solid.

(1*R*,1'*R*)/(1*S*,1'*S*) isomers:

yield: 48.4 mg, 0.0652 mmol, 49%, white solid

mp: 50.0 – 56.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.41 (d, *J* = 8.2 Hz, 1H, 14'-H or 10'-H), 7.21 (d, *J* = 7.9 Hz, 1H, 13-H), 7.13 (dd, *J* = 8.2, 2.6 Hz, 1H, 13'-H or 11'-H), 6.70 – 6.64 (m, 1H, 13'-H or 11'-H), 6.64 (s, 1H, 5'-H), 6.58 (dd, *J* = 8.0, 1.9 Hz, 1H, 14-H), 6.54 (d, *J* = 1.8 Hz, 1H, 10-H), 6.32 (s, 1H, 5-H), 6.21 (dd, *J* = 8.3, 2.2 Hz, 1H, 14'-H or 10'-H), 6.16 (s, 1H, 8'-H), 5.28 (d, *J* = 6.1 Hz, 1H, 1-H), 5.05 (s, 1H, 1'-H), 4.35 – 4.22 (m, 3H, 3-H, 'OC*H*$_2$-CH$_3$), 3.99 (ddd, *J* = 12.7, 5.7, 3.6 Hz, 1H, 3'-H), 3.87 – 3.76 (m, 2H, OC*H*$_2$-CH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.50 (dd, *J* = 11.9, 5.2 Hz, 1H, α'-H), 3.45 – 3.36 (m, 2H, 3-H, 3'-H), 3.35 (s, 3H, 6'-OCH$_3$), 3.25 (s, 3H, 7-OCH$_3$), 3.14 (ddd, *J* = 16.5, 11.2, 5.8 Hz, 1H, 4'-H), 2.93 – 2.77 (m, 2H, 4-H, 4'-H), 2.76 – 2.72 (m, 2H, α-H), 2.69 – 2.61 (m, 2H, 4-H, α'-H), 1.36 (t, *J* = 7.0 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.88 (br s, 3H, OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.9 (C=O or C=O'), 155.7 (C-11), 155.5 (C=O or C=O'), 153.8 (C-12'), 152.1 (C-6), 149.1 (C-6'), 147.0 (C-8), 144.8 (C-7'), 140.6 (C-9), 138.9 (C-7), 135.2 (C-9'), 132.3 (C-14' or C-10'), 130.2 (C-14' or C-10'), 130.2 (C-4a'), 129.7 (C-13), 128.7 (C-8a'), 128.2 (C-4a), 122.7 (C-14), 122.5 (C-8a), 121.9 (C-13' or C-11'), 121.4 (C-13' or C-11'), 120.3 (C-12), 119.6 (C-8'), 117.0 (C-10), 113.9 (C-5'), 107.4 (C-5), 61.4 ('O*C*H$_2$-CH$_3$), 60.8 (O*C*H$_2$-CH$_3$), 60.3 (7-OCH$_3$), 57.6 (C-1'), 56.9 (6'-OCH$_3$), 56.3 (6-OCH$_3$), 53.4 (C-

1), 41.9 (C-3' and C-α'), 41.1 (C-α), 36.7 (C-3), 27.9 (C-4 and C-4'), 14.8 ('OCH_2-*C*H_3), 14.1 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2853, 1692, 1505, 1417, 1277, 1205, 1105, 1023, 840, 765

Purity (HPLC, method c) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{43}{}^{35}ClN_2O_9 + H]^+$ 743.2730, found: 743.2735

(1*R*,1'*S*)/(1*S*,1'*R*) isomers:

yield: 54.3 mg, 0.0732 mmol, 55%, white solid

mp: 113.5 – 118.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.39 (d, *J* = 8.2 Hz, 1H, 14'-H or 10'-H), 7.18 (d, *J* = 7.9 Hz, 1H, 13-H), 7.09 (dd, *J* = 8.2, 2.5 Hz, 1H, 13'-H or 11'-H), 6.65 (s, 1H, 5'-H), 6.62 (dd, *J* = 8.4, 2.2 Hz, 2H, 13'-H or 11'-H), 6.58 (dd, *J* = 8.0, 1.8 Hz, 1H, 14-H), 6.43 – 6.37 (m, 2H, 10-H, 14'-H or 10'-H), 6.28 (s, 1H, 5-H), 6.18 (s, 1H, 8'-H), 5.25 (d, *J* = 8.2 Hz, 1H, 1-H), 5.11 (dd, *J* = 10.4, 6.2 Hz, 1H, 1'-H), 4.31 – 4.11 (m, 3H, 3, 'OC*H*$_2$-CH_3), 3.99 – 3.88 (m, 1H, 3'-H), 3.87 – 3.77 (m, 2H, OC*H*$_2$-CH_3), 3.73 (s, 3H, 6-OCH_3), 3.60 (s, 3H, 6'-OCH_3), 3.55 (dd, *J* = 11.8, 5.7 Hz, 1H, α'-H), 3.46 (td, *J* = 11.5, 4.9 Hz, 1H, 3'-H), 3.30 (td, *J* = 13.8, 12.9, 4.5 Hz, 1H, 3-H), 3.16 (s, 3H, 7-OCH_3), 3.19 – 3.08 (m, 2H, α-H, 4'-H), 2.82 (dt, *J* = 15.7, 4.6 Hz, 1H, 4'-H), 2.80 – 2.74 (m, 1H, 4-H), 2.72 (dd, *J* = 12.8, 10.6 Hz, 1H, α'-H), 2.63 – 2.54 (m, 1H, α-H), 2.47 (d, *J* = 16.8 Hz, 1H, 4-H), 1.33 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$), 0.98 (br s, 3H, OCH$_2$-C*H*$_3$)

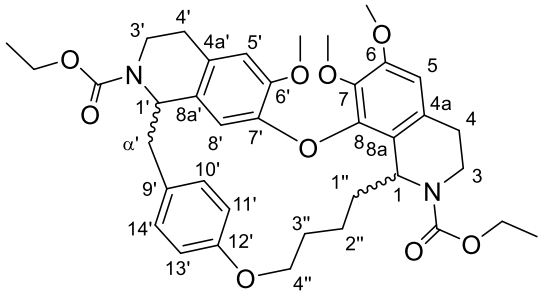
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.8 (C-11), 155.4 (C=O and C=O'), 153.8 (C-12'), 152.6 (C-6), 150.1 (C-6'), 144.0 (C-7'), 140.8 (C-9), 137.9 (C-7), 135.3 (C-9'), 131.6 (C-14' or C-10'), 130.6 (C-4a'), 130.2 (C-14' or C-10'), 129.6 (C-4a), 129.4 (C-13), 128.3 (C-8a'), 123.0 (C-14), 121.9 (C-13' and C-11'), 120.2 (C-8a and C-12), 119.6 (C-8'), 117.3 (C-10), 111.9 (C-5'), 106.9 (C-5), 61.4 ('O*C*H$_2$-CH_3), 61.0 (O*C*H$_2$-CH_3), 60.5 (7-OCH_3), 57.0 (C-1'), 56.2 (6-OCH_3), 56.1 (6'-OCH_3), 54.1 (C-1), 41.7 (C-3'), 41.5 (C-α'), 39.2 (C-α), 37.3 (C-3), 28.2 (C-4), 28.1 (C-4'), 14.8 ('OCH_2-*C*H_3), 14.2 (OCH_2-*C*H_3). The resonance of C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2936, 2828, 1692, 1506, 1416, 1276, 1204, 1099, 1022, 840, 768

Purity (HPLC, method c) = 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{41}H_{43}{}^{35}ClN_2O_9 + Na]^+$ 765.2549, found: 765.2550

(±)-*N*,*N'*-Bis-(ethoxycarbonyl) ring C-propylidene analogues of bisnortetrandrine and –isotetrandrine (**91**)



$C_{38}H_{46}N_2O_9$

M_W = 674.32 g/mol

Previously separated diastereomers of bisbenzylisoquinoline **85** (85 mg, 0.112 mmol of each diastereomer), potassium iodide (3.70 mg, 0.0225 mmol, 0.2 eq.) and potassium carbonate (37.2 mg, 0.225 mmol, 2.0 eq.) were dissolved in 6.0 mL of anhydrous DMF. The mixture was stirred for 48 h at 105 °C. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.25) and the products obtained as white solids.

Precursor of **RMS10**:

yield: 45.3 mg, 0.0672 mmol, 60%, white solid

mp: 103.5 – 104.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.24 (br s, 1H, 14'-H or 10'-H), 6.86 (br s, 1H, 13'-H or 11'-H), 6.65 (br s, 1H, 13'-H or 11'-H), 6.60 (s, 1H, 5'-H), 6.28 (s, 1H, 5-H), 6.20 (br s, 1H, 14'-H or 10'-H), 5.66 (s, 1H, 8'-H), 5.26 (d, *J* = 4.5 Hz, 1H, 1-H), 4.93 (dd, *J* = 10.0, 4.1 Hz, 1H, 1'-H), 4.28 – 4.18 (m, 3H, 4''-H, OC*H*$_2$-CH$_3$), 4.18 – 4.08 (m, 2H, 'OC*H*$_2$-CH$_3$), 4.04 – 3.96 (m, 2H, 3-H, 4''-H), 3.81 (dt, *J* = 12.4, 5.5 Hz, 1H, 3'-H), 3.70 (s, 3H, 6-OCH$_3$), 3.62 – 3.56 (m, 1H, 3'-H), 3.55 (s, 3H, 6'-OCH$_3$), 3.37 (dd, *J* = 12.2, 5.2 Hz, 1H, α'-H), 3.33 – 3.24 (m, 1H, 3-H), 3.13 (s, 3H, 7-OCH$_3$), 2.98 (ddd, *J* = 14.9, 9.0, 5.4 Hz, 1H, 4'-H), 2.88 – 2.75 (m, 2H, 4-H, 4'-H), 2.64 (dt, *J* = 16.2, 4.6 Hz, 1H, 4-H), 2.54 (t, *J* = 11.6 Hz, 1H, α'-H), 1.91 – 1.80 (m, 1H, 3''-H), 1.65 – 1.52 (m, 4H, 1''-H, 2''-H, 3''-H), 1.49 – 1.39 (m, 1H, 2''-H), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$-C*H*$_3$), 1.25 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$-C*H*$_3$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 158.0 (C-12'), 155.8 ('C=O), 155.7 (C=O), 152.3 (C-6), 149.6 (C-6'), 145.0 (C-7'), 138.2 (C-7), 131.7 (C-14' or C-10'), 129.6 (C-4a'), 129.5 (C-14' or C-10'), 128.1 (C-8a'), 123.3 (C-8a), 120.1 (C-8'), 116.9 (C-13' and C-11'), 113.2 (C-5'), 107.2 (C-5), 68.9 (C-4''), 61.3 (O*C*H$_2$-CH$_3$), 61.0 ('O*C*H$_2$-CH$_3$), 60.1 (7-OCH$_3$), 57.4 (C-1'), 56.8 (6'-OCH$_3$), 56.2 (6-OCH$_3$), 50.6 (C-1), 41.6 (C-α'), 40.9 (C-3'), 37.7 (C-3), 34.1 (C-1''), 28.6 (C-3''), 28.0 (C-4 and C-4'), 22.0 (C-2''), 14.8 (OCH$_2$-*C*H$_3$), 14.7 ('OCH$_2$-*C*H$_3$). The resonances of C-9', C-4a and C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 2840, 1689, 1509, 1415, 1273, 1207, 1099, 1023, 879, 769

Purity (HPLC, method c) = 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{46}N_2O_9 + H]^+$ 675.3276, found: 675.3288

Precursor of **RMS9**:

yield: 21.9 mg, 0.0325 mmol, 29%, white solid

mp: 178.0 °C

^{1}H NMR (400 MHz, TcI_2, 100 °C) δ [ppm] = 7.20 (d, *J* = 6.5 Hz, 1H, 14'-H or 10'-H), 6.96 (d, *J* = 6.7 Hz, 1H, 13'-H or 11'-H), 6.60 (s, 1H, 5'-H), 6.43 (d, *J* = 5.8 Hz, 1H, 13'-H or 11'-H), 6.28 (s, 1H, 5-H), 6.23 (d, *J* = 7.4 Hz, 1H, 14'-H or 10'-H), 5.90 (s, 1H, 8'-H), 5.16 (dd, *J* = 9.5, 2.0 Hz, 1H, 1-H), 4.98 (dd, *J* = 10.3, 5.6 Hz, 1H, 1'-H), 4.27 – 4.11 (m, 4H, 'OC*H*$_2$-CH_3, OC*H*$_2$-CH_3), 4.11 – 4.00 (m, 3H, 3-H, 4''-H), 3.87 – 3.78 (m, 1H, 3'-H), 3.72 (s, 3H, 6-OCH_3), 3.58 (s, 3H, 6'-OCH_3), 3.55 – 3.46 (m, 1H, 3'-H), 3.43 (dd, *J* = 12.7, 6.0 Hz, 1H, α'-H), 3.30 – 3.20 (m, 1H, 3-H), 3.15 (s, 3H, 7-OCH_3), 3.06 (ddd, *J* = 15.5, 9.8, 5.5 Hz, 1H, 4'-H), 2.88 – 2.74 (m, 2H, 4-H, 4'-H), 2.67 – 2.55 (m, 2H, 4-H, α'-H), 1.81 – 1.70 (m, 2H, 1''-H, 3''-H), 1.69 – 1.59 (m, 1H, 1''-H), 1.58 – 1.49 (m, 1H, 3''-H), 1.48 – 1.38 (m, 1H, 2''-H), 1.36 – 1.24 (m, 7H, 2''-H, 'OCH$_2$-C*H*$_3$, OCH$_2$-C*H*$_3$)

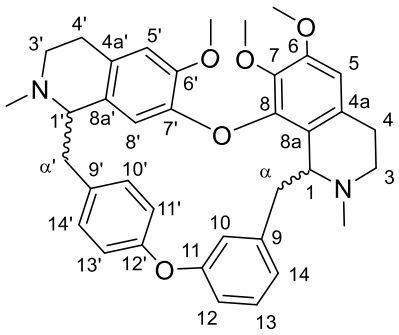
^{13}C NMR (101 MHz, TcI_2, 100 °C) δ [ppm] = 156.4 (C-12'), 155.9 (C=O or C=O'), 155.7 (C=O or C=O'), 152.2 (C-6), 149.9 (C-6'), 144.7 (C-7'), 138.2 (C-7), 130.9 (C-14' or C-10'), 130.1 (C-4a'), 129.4 (C-14' or C-10'), 128.6 (C-8a'), 121.8 (C-8a), 119.7 (C-8'), 112.3 (C-5'), 107.1 (C-5), 68.7 (C-4''), 61.3 ('O*C*H$_2$-CH_3 or O*C*H$_2$-CH_3), 61.2 ('O*C*H$_2$-CH_3 or O*C*H$_2$-CH_3) , 60.4 (7-OCH_3), 57.1 (C-1'), 56.4 (6'-OCH_3), 56.3 (6-OCH_3), 50.3 (C-1), 41.4 (C-α'), 41.3 (C-3'), 37.7 (C-3), 33.5 (C-1''), 28.3 (C-4), 28.1 (C-4'), 27.4 (C-3''), 21.4 (C-2''), 14.8 (OCH$_2$-*C*H_3), 14.8 ('OCH$_2$-*C*H_3). The resonances of C-9', C-4a and C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2860, 1690, 1508, 1414, 1275, 1203, 1098, 1023, 768

Purity (HPLC, method c) = 83% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{46}N_2O_9 + H]^+$ 675.3276, found: 675.3274

(±)-12-Desmethoxytetrandrine and –isotetrandrine - **RMS1-2**



$C_{37}H_{40}N_2O_5$

M_W = 592.29 g/mol

RMS1: (1*R*,1'*S*)/(1*S*,1'*R*) isomers of carbamate **86** (17.0 mg, 0.024 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.0% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.14) affording the product as a beige solid.

yield: 13 mg, 0.0219 mmol, 91%, beige solid

mp: 196.5 – 198.0 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.28 (dd, *J* = 8.3, 2.1 Hz, 1H, 10'-H or 14'-H), 7.18 (t, *J* = 7.8 Hz, 1H, 13-H), 7.07 (dd, *J* = 8.1, 2.5 Hz, 1H, 11'-H or H-13'), 6.96 (dd, *J* = 8.1, 2.5 Hz, 1H, 12-H), 6.85 (d, *J* = 7.4 Hz, 1H, 14-H), 6.62 (dd, *J* = 8.2, 1.7 Hz, 1H, 11'-H or 13'-H), 6.53 (s, 1H, 5'-H), 6.45 – 6.37 (m, 2H, 10-H, 10'-H or 14'-H), 6.28 (s, 1H, 5-H), 5.99 (s, 1H, 8'-H), 3.92 – 3.82 (m, 2H, 1-H, 1'-H), 3.75 (s, 3H, 6-OCH_3), 3.60 (s, 3H, 6'-OCH_3), 3.45 – 3.36 (m, 1H, 3'-H), 3.33 – 3.21 (m, 2H, α'-H, 3-H), 3.12 (s, 3H, 7-OCH_3), 3.07 (d, *J* = 13.9 Hz, 1H, α-H), 2.96 – 2.88 (m, 2H, α'-H, 4'-H), 2.86 – 2.75 (m, 4H, 3-H, 3'-H, 4-H, 4'-H), 2.68 – 2.61 (m, 1H, α-H), 2.58 (s, 3H, 2'-NCH_3), 2.43 – 2.34 (m, 1H, 4-H), 2.25 (s, 3H, 2-NCH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 160.4 (C-11), 154.3 (C-12'), 152.0 (C-6), 150.0 (C-6'), 144.5 (C-9), 143.7 (C-7'), 137.2 (C-7), 135.4 (C-9'), 132.3 (C-10' or 14'), 130.3 (C-10' or 14'), 129.1 (C-13), 127.9 (C-8a'), 123.4 (C-14), 122.0 (C-11' or 13'), 121.5 (C-11' or 13'), 121.0 (C-8a), 120.0 (C-8'), 115.3 (C-10), 115.1 (C-12), 111.3 (C-5'), 105.6 (C-5), 63.9 (C-1'), 62.1 (C-1), 60.7 (7-OCH_3), 55.9 (6-OCH_3), 55.7 (6'-OCH_3), 46.2 (C-3'), 45.4 (C-3), 43.0 (2'-N*C*H_3), 42.9 (2-N*C*H_3), 39.4 (C-α), 37.9 (C-α'), 25.9 (C-4'), 23.7 (C-4). The resonances of C-8, C-4a and C-4a' could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2923, 2853, 1740, 1606, 1506, 1462, 1255, 1114, 1018, 841, 698

Purity (HPLC, method c) = 99%, d.r. > 99:1 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{37}H_{40}N_2O_5 + H]^+$ 593.3010, found: 593.3011

RMS2: (1*R*,1'*R*)/(1*S*,1'*S*) isomers of carbamate **86** (47.0 mg, 0.0663 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.0% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.14) affording the product as a white solid.

yield: 37 mg, 0.0624 mmol, 94%, white solid

mp: 206.0 – 206.5 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.35 (dd, *J* = 8.2, 2.2 Hz, 1H, 10'-H or 14'-H), 7.23 (t, *J* = 7.8 Hz, 1H, 13-H), 7.11 (dd, *J* = 8.1, 2.6 Hz, 1H, 11'-H or 13'-H), 6.99 (dd, *J* = 7.8, 2.3 Hz, 1H, 12-H), 6.97 (s, 1H, 14-H), 6.77 (dd, *J* = 8.3, 2.6 Hz, 1H, 11'H or 13'-H), 6.55 (t, *J* = 1.9 Hz, 1H, 10-H), 6.51 (s, 1H, 5'-H), 6.31 (s, 1H, 5-H), 6.30 – 6.28 (m, 1H, 10'-H or 14'-H), 5.99 (s, 1H, 8'-H), 3.92 – 3.86 (m, 1H, 1'-H), 3.78 (d, *J* = 8.7 Hz, 1H, 1-H), 3.75 (s, 3H, 6-OCH_3), 3.56 – 3.48 (m, 1H, 3-H), 3.49 – 3.42 (m, 1H, 3'-H), 3.37 (s, 3H, 6'-OCH_3), 3.32 – 3.25 (m, 1H, α'-H), 3.18 (s, 3H, 7-OCH_3), 2.99 – 2.87 (m, 4H, 3-H, 3'-H, 4-H, 4'-H), 2.80 (t, *J* = 11.7 Hz, 1H, α'-H), 2.77 – 2.72 (m, 2H, α-H, 4'-H), 2.63 (s, 3H, 2'-NCH_3), 2.59 – 2.52 (m, 1H, α-H), 2.49 – 2.38 (m, 1H, 4-H), 2.34 (s, 3H, 2-NCH_3)

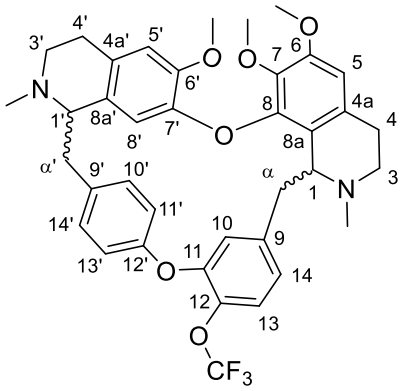
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 160.2 (C-11), 154.1 (C-12'), 151.6 (C-6), 148.8 (C-6'), 144.0 (C-7'), 143.9 (C-9), 138.0 (C-7), 135.1 (C-9'), 132.8 (C-10' or C-14'), 130.3 (C-10' or 14'), 129.2 (C-13), 128.0 (C-8a'), 123.3 (C-14), 123.1 (C-8a), 122.0 (C-11' or C-13'), 121.8 (C-11' or C-13'), 120.4 (C-8'), 115.6 (C-10), 115.2 (C-12), 112.8 (C-5'), 105.9 (C-5), 64.1 (C-1'), 61.5 (C-1), 60.4 (7-OCH_3), 56.0 (6'-OCH_3 or 6-OCH_3), 55.9 (6'-OCH_3 or 6-OCH_3), 45.4 (C-3'), 44.2 (C-3), 42.8 (C-α), 42.7 (2'-NCH_3), 42.4 (2-NCH_3), 38.5 (C-α'), 25.2 (C-4'), 22.2 (C-4). The resonances of C-8, C-4a and C-4a' could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2926, 2841, 1586, 1505, 1268, 1211, 1111, 1023, 841, 785

Purity (HPLC, method c) = 99%, d.r. 95:5 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{37}H_{40}N_2O_5 + H]^+$ 593.3010, found: 593.3011

(±)-12-Desmethoxy-12-trifluoromethoxytetrandrine and –isotetrandrine - **RMS3-4**



$C_{38}H_{39}F_3N_2O_6$

M_W = 676.28 g/mol

RMS3: (1*R*,1'*S*)/(1*S*,1'*R*) isomers of carbamate **87** (13.0 mg, 0.0164 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.5% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.11) affording the product as a white solid.

yield: 9.7 mg, 0.0143 mmol, 87%, white solid

mp: 111.0 – 112.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.30 (dd, *J* = 8.2, 2.1 Hz, 1H, 10'-H or 14'-H), 7.12 (d, *J* = 8.3 Hz, 1H, 13-H), 7.08 (d, *J* = 8.5 Hz, 1H, 11'-H or 13'-H), 6.83 (dd, *J* = 8.2, 1.5 Hz, 1H, 14-H), 6.64 – 6.57 (m, 2H, 10-H, 11'-H or 13'-H), 6.53 (s, 1H, 5'-H), 6.45 (br s, 1H, 10'-H or 14'-H), 6.27 (s, 1H, 5-H), 5.97 (s, 1H, 8'-H), 3.90 – 3.84 (m, 1H, 1'-H), 3.82 (d, *J* = 9.6 Hz, 1H, 1-H), 3.75 (s, 3H, 6-OCH_3), 3.60 (s, 3H, 6'-OCH_3), 3.45 – 3.35 (m, 1H, 3'-H), 3.25 (dd, *J* = 12.9, 6.3 Hz, 2H, α'-H, 3-H), 3.13 (s, 3H, 7-OCH_3), 3.05 (d, *J* = 13.8 Hz, 1H,α-H), 2.96 – 2.87 (m, 1H, α'-H, 4'-H), 2.87 – 2.75 (m, 4H, 3'-H, 3-H, 4-H, 4'-H), 2.63 (dd, *J* = 10.2, 3.6 Hz, 1H, α-H), 2.58 (s, 3H, 2'-NCH_3), 2.42 – 2.31 (m, 1H, 4-H), 2.26 (s, 3H, 2-NCH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 153.7 (C-12'), 152.3 (C-11), 152.1 (C-6), 149.9 (C-6'), 143.6 (C-7'), 143.4 (C-9), 137.2 (C-7), 136.1 (C-12), 136.0 (C-9'), 132.4 (C-10' or C-14'), 130.5 (C-10' or C-14'), 127.8 (C-8a'), 123.3 (C-14), 122.5 (C-13), 121.8 (C-11' or C-13'), 121.5 (C-11' or C-13'), 120.4 (C-8a), 119.9 (C-8'), 117.2 (C-10), 111.3 (C-5'), 105.6 (C-5), 63.8 (C-1'), 62.2 (C-1), 60.7 (7-OCH_3), 55.9 (6-OCH_3), 55.7 (6'-OCH_3), 46.1 (C-3'), 45.3 (C-3), 42.9 (2'-NCH_3), 42.7 (2-NCH_3), 39.2 (C-α), 37.7 (C-α'), 25.9 (C-4'), 22.8 (C-4). The resonances of C-8, C-4a, C-4a' and OCF_3 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2933, 2843, 1593, 1505, 1416, 1198, 1164, 1112, 1008, 838, 729

Purity (HPLC, method c) = 98%, d.r. 95:5 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{39}F_3N_2O_6 + H]^+$ 677.2833, found: 677.2838

RMS4: (1*R*,1'*R*)/(1*S*,1'*S*) isomers of carbamate **87** (32.0 mg, 0.0404 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.5% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.11) affording the product as a white solid.

yield: 20.2 mg, 0.0298 mmol, 74%, white solid

mp: 174.0 – 176.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.36 (dd, *J* = 8.2, 2.2 Hz, 1H, 10'-H or 14'-H), 7.17 (d, *J* = 8.1 Hz, 1H, 13-H), 7.12 (dd, *J* = 8.2, 2.6 Hz, 1H, 11'-H or 13'-H), 6.94 (d, *J* = 8.2 Hz, 1H, 14-H), 6.76 (dd, *J* = 8.3, 2.6 Hz, 1H, 11'-H or 13'-H), 6.63 (d, *J* = 1.9 Hz, 1H, 10-H), 6.51 (s, 1H, 5'-H), 6.31 (s, 1H, 5-H), 6.32 – 6.28 (m, 1H, 10'-H or 14'-H), 5.98 (s, 1H, 8'-H), 3.89 (dd, *J* = 10.9, 5.7 Hz, 1H, 1'-H), 3.75 (s, 3H, 6-OCH_3), 3.72 (s, 1H, 1-H), 3.55 – 3.43 (m, 2H, 3-H, 3'-H), 3.38 (s, 3H, 6'-OCH_3), 3.31 – 3.24 (m, 1H, α'-H), 3.18 (s, 3H, 7-OCH_3), 3.00 – 2.85 (m, 4H, 3-H, 3'-H, 4-H, 4'-H), 2.83 (d, *J* = 11.7 Hz, 1H, α'-H), 2.79 – 2.70 (m, 2H, α-H, 4'-H), 2.63 (s, 3H, 2'-NCH_3), 2.54 (d, *J* = 13.6 Hz, 1H, α-H), 2.41 (dd, *J* = 11.3, 5.2 Hz, 1H, 4-H), 2.34 (s, 3H, 2-NCH_3)

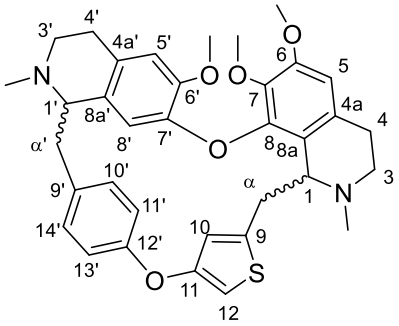
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 153.6 (C-12'), 152.2 (C-11), 151.7 (C-6), 148.8 (C-6'), 148.6 (C-8), 143.9 (C-7'), 142.6 (C-9), 138.0 (C-7), 136.2 (C-12), 135.7 (C-9'), 133.0 (C-10' or 14'), 130.4 (C-10' or 14'), 128.3 (C-4a'), 128.2 (C-4a), 127.9 (C-8a'), 123.2 (C-14), 122.7 (C-8a and 13), 121.8 (C-11' or C-13'), 121.7 (C-11' or C-13'), 121.0 (q, *J* = 257.2 Hz, OCF_3), 120.3 (C-8'), 117.7 (C-10), 112.7 (C-5'), 106.0 (C-5), 64.1 (C-1'), 61.3 (C-1), 60.4 (7-OCH_3), 55.9 (6'-OCH_3 and 6-OCH_3), 45.4 (C-3'), 44.1 (C-3), 42.7 (2'-NCH_3), 42.3 (C-α), 42.3 (2-NCH_3), 38.3 (C-α'), 25.3 (C-4'), 21.9 (C-4)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2926, 2846, 1596, 1504, 1250, 1200, 1163, 1113, 1020, 840

Purity (HPLC, method c) = 99%, d.r. 94:6 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{39}F_3N_2O_6 + H]^+$ 677.2833, found: 677.2839

(±)-Ring C thiophene analogues of tetrandrine and –isotetrandrine - RMS5-6



$C_{35}H_{38}N_2O_5S$

M_W = 598.25 g/mol

RMS5: (1*R*,1'*S*)/(1*S*,1'*R*) isomers of carbamate **89** (10.0 mg, 0.014 mmol) were reduced following General Procedure 4. The reaction was completed after 4 h. Purification by flash column chromatography (ethyl acetate → 2.0% trimethylamine in ethyl acetate, R_f = 0.08) affording the product as a beige solid.

yield: 5.2 mg, 0.0087 mmol, 62%, beige solid

mp: 149.0 – 151.0 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.27 – 7.24 (m, 1H, 14'-H or 10'-H), 7.10 (dd, *J* = 8.1, 2.6 Hz, 1H, 13'-H or 11'-H), 6.64 (dd, *J* = 8.3, 2.6 Hz, 1H, 13'-H or 11'-H), 6.48 (s, 1H, 5'-H), 6.48 – 6.43 (m, 1H, 14'-H or 10'-H), 6.35 (d, *J* = 1.7 Hz, 1H, 12-H), 6.26 (s, 1H, 5-H), 6.02 (s, 2H, 10-H, 8'-H), 3.94 (d, *J* = 7.6 Hz, 1H, 1-H), 3.91 – 3.85 (m, 1H, 1'-H), 3.74 (s, 3H, 6-OCH_3), 3.52 (s, 3H, 6'- OCH_3), 3.50 – 3.43 (m, 1H, 3'-H), 3.28 (dd, *J* = 12.9, 7.0 Hz, 1H, α'-H), 3.17 – 3.11 (m, 2H, 3-H, α-H), 3.09 (s, 3H, 7- OCH_3), 2.96 (t, *J* = 11.0 Hz, 1H, α'-H), 2.93 – 2.73 (m, 6H, 3-H, 4-H, α-H, 4'-H, 3'-H), 2.56 (s, 3H, 2'-NCH_3), 2.49 (d, *J* = 19.4 Hz, 1H, 4-H), 2.37 (s, 3H, 2-NCH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 157.3 (C-11), 156.6 (C-12'), 152.0 (C-6), 149.8 (C-6'), 144.5 (C-9), 143.2 (C-7'), 136.8 (C-7), 135.4 (C-9'), 132.1 (C-14' or C-10'), 130.1 (C-14' or C-10'), 129.4 (C-4a), 129.1 (C-4a'), 127.5 (C-8a'), 121.9 (C-13' or C-11'), 121.0 (C-13' or C-11'), 120.7 (C-8a), 120.0 (C-8'), 117.6 (C-10), 111.3 (C-5'), 105.2 (C-5), 99.7 (C-12), 64.1 (C-1'), 63.2 (C-1), 60.7 (7-OCH_3), 55.9 (6-OCH_3), 55.6 (6'-OCH_3), 46.2 (C-3'), 44.8 (C-3), 43.1 (2'-NCH_3), 43.0 (2-NCH_3), 38.1 (C-α'), 33.8 (C-α), 25.5 (C-4'), 24.8 (C-4). The resonance of C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 2853, 1736, 1556, 1507, 1451, 1261, 1106, 1017, 798

Purity (HPLC, method c) = 98%, d.r. >99:1 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{35}H_{38}N_2O_5S + H]^+$ 599.2574, found: 599.2574

RMS6: (1*R*,1'*R*)/(1*S*,1'*S*) isomers of carbamate **89** (20.0 mg, 0.028 mmol) were reduced following General Procedure 4. The reaction was completed after 2 h. Purification by flash column chromatography (ethyl acetate → 2.0% trimethylamine in ethyl acetate, R_f = 0.08) affording the product as a beige solid.

yield: 12.9 mg, 0.0215 mmol, 77%, beige solid

mp: 251.5 – 252.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.31 (dd, *J* = 8.2, 2.2 Hz, 1H, 14'-H or 10'-H), 7.13 (dd, *J* = 8.1, 2.6 Hz, 1H, 13'-H or 11'-H), 6.78 (dd, *J* = 8.3, 2.6 Hz, 1H, 13'-H or 11'-H), 6.50 (s, 1H, 5'-H), 6.44 (d, *J* = 1.7 Hz, 1H, 12-H), 6.29 (s, 1H, 5-H), 6.26 (dd, *J* = 8.3, 2.2 Hz, 1H, 14'-H or 10'-H), 6.24 (d, *J* = 1.7 Hz, 1H, 10-H), 5.90 (s, 1H, 8'-H), 3.93 (d, *J* = 7.2 Hz, 1H, 1-H), 3.79 (dd, *J* = 11.2, 5.5 Hz, 1H, 1'-H), 3.74 (s, 3H, 6-OCH_3), 3.52 – 3.43 (m, 1H, 3'-H), 3.36 (s, 3H, 6'-OCH_3), 3.31 – 3.21 (m, 2H, 3-H, α'-H), 3.13 (s, 3H, 7-OCH_3), 3.00 – 2.82 (m, 5H, 3-H, 4-H, α-H, 4'-H, 3'-H), 2.83 – 2.72 (m, 2H, α-H, α '-H), 2.76 – 2.67 (m, 1H, 4'-H), 2.58 (s, 3H, 2'-NCH_3), 2.46 (s, 3H, 2-NCH_3), 2.46 – 2.35 (m, 1H, 4-H)

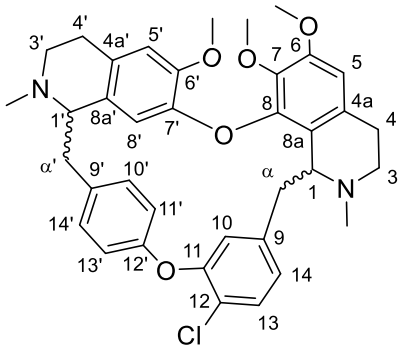
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.9 (C-12'), 156.8 (C-11), 151.8 (C-6), 148.9 (C-6'), 148.9 (C-8), 144.3 (C-7'), 143.7 (C-9), 138.2 (C-7), 135.1 (C-9'), 132.7 (C-14' or C-10'), 129.9 (C-14' or C-10'), 128.5 (C-4a'), 128.0 (C-8a'), 123.7 (C-8a), 121.6 (C-13' or C-11'), 121.0 (C-13' or C-11'), 120.7 (C-8'), 118.5 (C-10), 112.9 (C-5'), 106.0 (C-5), 100.9 (C-12), 64.5 (C-1'), 61.8 (C-1), 60.3 (7-OCH_3), 55.9 (6-OCH_3), 55.9 (6'-OCH_3), 45.4 (C-3'), 44.5 (C-3), 42.8 (2'-NCH_3), 42.5 (2-NCH_3), 39.0 (C-α'), 37.5 (C-α), 24.9 (C-4'), 23.2 (C-4). The resonance of C-4a could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2853, 1561, 1505, 1357, 1262, 1205, 1102, 1015, 809, 717

Purity (HPLC, method c) = 97%, d.r. 96:4 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{35}H_{38}N_2O_5S + H]^+$ 599.2574, found: 599.2580

(±)-12-Desmethoxy-12-chlorotetrandrine and –isotetrandrine - **RMS7-8**



$C_{37}H_{39}ClN_2O_5$

M_W = 626.26 g/mol

RMS7: A solution of the (1*R*,1'*S*)/(1*S*,1'*R*) isomers of carbamate **90** (40.0 mg, 0.0538 mmol) in 1.0 mL anhydrous THF was cooled to 0 °C and methyllithium (1.6 M solution in diethyl ether; 0.510 mL, 0.807 mmol, 15 eq.) was added slowly. The mixture was stirred at 0 °C for 4 h and was then quenched with 1.0 mL deionized water. After alkalizing to pH 12–14 with 2.0 M NaOH solution, the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the secondary amine as a yellow oil. The crude amine was dissolved in 1.0 mL methanol, a solution of formaldehyde (37% in water; 20.0 µL, 0.269 mmol, 5 eq.), one drop of acetic acid and sodium cyanoborohydride (10.7 mg, 0.161 mmol, 3 eq.) was added. The mixture was stirred at ambient temperature for 12 h and the volatiles removed *in vacuo*. Purification by flash column chromatography (ethyl acetate → 3.0% trimethylamine in ethyl acetate, R_f = 0.16) afforded the product as a white solid.

yield: 9.9 mg, 0.0159 mmol, 30%, white solid

mp: 227.5 – 230.0 °C

^{1}H NMR (800 MHz, $CDCl_3$) δ [ppm] = 7.30 (d, *J* = 6.3 Hz, 1H, 14'-H or 10'-H), 7.25 – 7.22 (m, 1H, 13-H), 7.09 (d, *J* = 7.0 Hz, 1H, 13'-H or 11'-H), 6.79 (d, *J* = 8.2 Hz, 1H, 14-H), 6.62 (s, 1H, 13'-H or 11'-H), 6.54 (s, 2H, 10-H, 5'-H), 6.44 (s, 1H, 14'-H or 10'-H), 6.27 (s, 1H, 5-H), 5.97 (s, 1H, 8'-H), 3.87 (s, 1H, 1'-H), 3.80 (s, 1H, 1-H), 3.75 (s, 3H, 6-OCH_3), 3.61 (s, 3H, 6'-OCH_3), 3.40 (s, 1H, 3'-H), 3.26 (s, 2H, 3-H, α'-H), 3.13 (s, 3H, 7-OCH_3), 3.03 (d, *J* = 13.9 Hz, 1H, α-H), 2.92 (dt, *J* = 16.2, 6.1 Hz, 3H, 4-H, 4'-H, α'-H), 2.88 – 2.78 (m, 3H, 3-H, 4'-H, 3'-H), 2.66 – 2.54 (m, 2H, α-H), 2.58 (s, 3H, 2'-NCH_3), 2.44 – 2.30 (m, 1H, 4-H), 2.24 (s, 3H, 2-NCH_3)

^{13}C NMR (201 MHz, $CDCl_3$) δ [ppm] = 155.7 (C-11), 153.8 (C-12'), 152.1 (C-6), 150.0 (C-6'), 143.7 (C-7'), 137.1 (C-7), 132.4 (C-14' or C-10'), 130.5 (C-14' or C-10'), 129.5 (C-13), 129.0 (C-4a'), 127.6 (C-8a'), 124.1 (C-14), 122.1 (C-13' and C-11'), 120.6 (C-8a), 119.9 (C-8'), 119.5 (C-12), 116.5 (C-10), 111.4 (C-5'), 105.7 (C-5), 63.7 (C-1'), 62.1 (C-1), 60.6 (7-OCH_3), 55.9 (6-

OCH_3), 55.7 (6'-OCH_3), 46.1 (C-3'), 42.8 (2-NCH_3 and 2'-NCH_3), 39.1 (C-α), 37.9 (C-α'), 25.8 (C-4').The resonances of C-4a, C-8, C-9 and C-9' could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2799, 1579, 1505, 1412, 1262, 1205, 1113, 1021, 817

Purity (HPLC, method c) = 96%, d.r. >99:1 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{37}H_{39}{}^{35}ClN_2O_5 + H]^+$ 627.2620, found: 627.2621

RMS8: The (1*R*,1'*R*)/(1*S*,1'*S*) isomers of carbamate **90** (40.0 mg, 0.0538 mmol) were reacted and purified as described above for **RMS7** to afford the desired product as a white solid.

yield: 10.8 mg, 0.0172 mmol, 32%, white solid

mp: 148.0 – 150.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.36 (dd, *J* = 8.2, 2.2 Hz, 1H, 14'-H or 10'-H), 7.28 (d, *J* = 8.0 Hz, 1H, 13-H), 7.14 (dd, *J* = 8.2, 2.6 Hz, 1H, 13'-H or 11'-H), 6.90 (dd, *J* = 8.1, 1.9 Hz, 1H, 14-H), 6.76 (dd, *J* = 8.3, 2.6 Hz, 1H, 13'-H or 11'-H), 6.59 (d, *J* = 1.8 Hz, 1H, 10-H), 6.51 (s, 1H, 5'-H), 6.30 (s, 1H, 5-H), 6.30 (dd, *J* = 8.6, 2.1 Hz, 2H, 14'-H or 10'-H), 5.98 (s, 1H, 8'-H), 3.88 (dd, *J* = 10.9, 5.6 Hz, 1H, 1'-H), 3.75 (s, 3H, 6-OCH_3), 3.71 (d, *J* = 9.9 Hz, 1H, 1-H), 3.51 – 3.42 (m, 2H, 3-H, 3'-H), 3.37 (s, 3H, 6'-OCH_3), 3.27 (dd, *J* = 12.3, 5.7 Hz, 1H, α'-H), 3.18 (s, 3H, 7-OCH_3), 2.94 (qd, *J* = 19.6, 17.5, 7.8 Hz, 4H, 3-H, 4-H, 4'-H, 3'-H), 2.81 (t, *J* = 11.7 Hz, 1H, α'-H), 2.77 – 2.68 (m, 2H, α-H, 4'-H), 2.62 (s, 3H, 2'-NCH_3), 2.53 (d, *J* = 13.6 Hz, 1H, α-H), 2.44 – 2.37 (m, 1H, 4-H), 2.32 (s, 3H, 2-NCH_3)

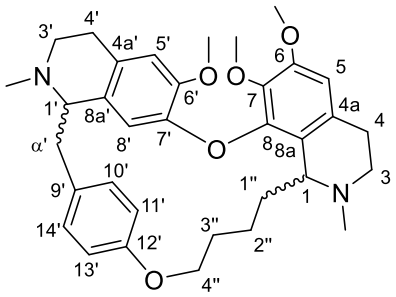
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 155.4 (C-11), 153.5 (C-12'), 151.5 (C-6), 148.7 (C-6'), 143.8 (C-7'), 142.3 (C-9), 137.9 (C-7), 135.6 (C-9'), 132.8 (C-14' or C-10'), 130.3 (C-14' or C-10'), 129.5 (C-13), 128.2 (C-4a'), 127.9 (C-8a'), 123.9 (C-14), 122.6 (C-8a), 121.7 (C-13' and C-11'), 120.2 (C-8'), 119.6 (C-12), 117.1 (C-10), 112.7 (C-5'), 105.8 (C-5), 63.9 (C-1'), 61.3 (C-1), 60.3 (7-OCH_3), 55.8 (6-OCH_3 and 6'-OCH_3), 45.2 (C-3'), 44.0 (C-3), 42.6 (2'-NCH_3), 42.2 (2-NCH_3), 42.1 (C-α), 38.2 (C-α'), 25.2 (C-4'), 21.8 (C-4). The resonances of C-8 and C-4a could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2922, 1747, 1578, 1505, 1413, 1266, 1206, 1111, 1019, 836

Purity (HPLC, method c) = 95%, d.r. > 99:1 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{37}H_{39}{}^{35}ClN_2O_5 + H]^+$ 627.2620, found: 627.2622

(±)-Ring C propylidene analogues of tetrandrine and –isotetrandrine - RMS9-10



$C_{34}H_{42}N_2O_5$

M_W = 558.31 g/mol

RMS9: The first fraction of separated diastereomers of carbamate **91** (20.0 mg, 0.0297 mmol) was reduced following General Procedure 4. The reaction was completed after 5 h. Purification by flash column chromatography (ethyl acetate → 3.0% trimethylamine in ethyl acetate, R_f = 0.15) afforded the product as a white solid.

yield: 14.7 mg, 0.0264 mmol, 89%, white solid

mp: 92.0 – 94.0 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.09 (dd, J = 8.3, 2.2 Hz, 1H, 14'-H or 10'-H), 6.96 (dd, J = 8.2, 2.6 Hz, 1H, 13'-H or 11'-H), 6.64 (s, 1H, 5'-H), 6.51 (dd, J = 8.4, 2.8 Hz, 1H, 13'-H or 11'-H), 6.33 (s, 1H, 5-H), 6.12 (dd, J = 8.4, 2.2 Hz, 1H, 14'-H or 10'-H), 5.42 (s, 1H, 8'-H), 4.27 (dt, J = 11.9, 4.5 Hz, 1H, 4''-H), 4.03 (ddd, J = 12.3, 9.2, 3.7 Hz, 1H, 4''-H), 3.84 (s, 3H, 6'-OCH_3), 3.73 (s, 3H, 6-OCH_3), 3.56 (dd, J = 10.6, 5.7 Hz, 1H, 1'-H), 3.41 – 3.33 (m, 1H, 3'-H), 3.30 – 3.21 (m, 2H, 1-H, 3-H), 3.15 (s, 3H, 7-OCH_3), 3.14 – 3.10 (m, 1H, α'-H), 2.92 – 2.83 (m, 2H, 4-H, 4'-H), 2.83 – 2.77 (m, 3H, 3-H, 4'-H, 3'-H), 2.70 (dd, J = 12.7, 10.6 Hz, 1H, α'-H), 2.51 (s, 3H, 2'-NCH_3), 2.45 (s, 3H, 2-NCH_3), 2.44 – 2.38 (m, 1H, 4-H), 1.78 – 1.68 (m, 2H, 3''-H, 2''-H), 1.66 – 1.53 (m, 2H, 3''-H, 1''-H), 1.48 – 1.36 (m, 2H, 2''-H, 1''-H)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 155.4 (C-12'), 152.0 (C-6), 150.5 (C-6'), 145.5 (C-7'), 138.6 (C-7), 131.9 (C-14' or C-10'), 131.1 (C-9'), 129.7 (C-14' or C-10'), 129.2 (C-4a), 128.9 (C-4a'), 128.3 (C-8a'), 123.2 (C-8a), 120.5 (C-8'), 119.0 (C-13' or C-11'), 115.6 (C-13' or C-11'), 112.0 (C-5'), 107.4 (C-5), 68.1 (C-4''), 64.5 (C-1'), 60.3 (7-OCH_3), 57.9 (C-1), 56.4 (6'-OCH_3), 55.9 (6-OCH_3), 46.1 (C-3'), 44.1 (C-3), 42.8 (2'-NCH_3), 41.9 (2-NCH_3), 38.2 (C-α'), 33.9 (C-1''), 26.8 (C-3''), 25.7 (C-4'), 22.7 (C-4), 21.4 (C-2''). The resonance of C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2850, 1607, 1508, 1451, 1266, 1216, 1010, 832, 750

Purity (HPLC, method c) = 96%, d.r. > 99:1 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{34}H_{42}N_2O_5 + H]^+$ 559.3166, found: 559.3163

RMS10: The second fraction of separated diastereomers of carbamate **91** (18.0 mg, 0.0267 mmol) was reduced following General Procedure 4. The reaction was completed after 5 h. Purification by flash column chromatography (ethyl acetate → 3.0% trimethylamine in ethyl acetate, R_f = 0.15) afforded the product as a white solid.

yield: 10.4 mg, 0.0186 mmol, 70%, white solid

mp: 153.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.22 (dd, *J* = 8.3, 2.3 Hz, 1H, 14'-H or 10'-H), 6.89 (dd, *J* = 8.3, 2.7 Hz, 1H, 13'-H or 11'-H), 6.72 (dd, *J* = 8.3, 2.7 Hz, 1H, 13'-H or 11'-H), 6.48 (s, 1H, 5'-H), 6.29 (dd, *J* = 8.3, 2.2 Hz, 1H, 14'-H or 10'-H), 6.25 (s, 1H, 5-H), 5.53 (s, 1H, 8'-H), 4.29 (dt, *J* = 9.9, 4.6 Hz, 1H, 4''-H), 4.06 (ddd, *J* = 11.7, 9.0, 3.2 Hz, 1H, 4''-H), 3.77 – 3.73 (m, 1H, 1'-H), 3.72 (s, 3H, 6-OCH_3), 3.66 (dd, *J* = 8.2, 3.6 Hz, 1H, 1-H), 3.51 (s, 3H, 6'-OCH_3), 3.40 – 3.25 (m, 2H, 3-H, 3'-H), 3.22 (dd, *J* = 12.6, 5.0 Hz, 1H, α'-H), 3.05 (s, 3H, 7-OCH_3), 3.00 – 2.77 (m, 4H, 3-H, 4-H, 4'-H, 3'-H), 2.71 – 2.61 (m, 2H, 4'-H, α'-H), 2.59 (s, 3H, 2'-NCH_3), 2.44 (s, 3H, 2-NCH_3), 2.38 (dd, *J* = 16.3, 5.7 Hz, 1H, 4-H), 1.91 – 1.81 (m, 1H, 3''-H), 1.73 – 1.56 (m, 3H, 3''-H, 2''-H), 1.55 – 1.45 (m, 2H, 1''-H)

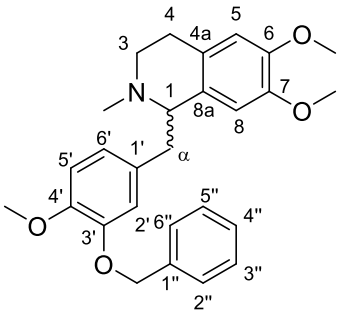
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 158.1 (C-12'), 151.7 (C-6), 149.1 (C-6'), 148.7 (C-8), 143.6 (C-7'), 137.3 (C-7), 132.4 (C-14' or C-10'), 131.4 (C-9'), 129.7 (C-14' or C-10'), 128.4 (C-4a'), 128.3 (C-4a), 127.9 (C-8a'), 122.6 (C-8a), 121.0 (C-8'), 117.2 (C-13' or C-11'), 116.0 (C-13' or C-11'), 111.7 (C-5'), 105.8 (C-5), 68.6 (C-4''), 64.3 (C-1'), 60.2 (7-OCH_3), 58.9 (C-1), 55.9 (6-OCH_3), 55.8 (6'-OCH_3), 45.4 (C-3'), 43.9 (C-3), 42.6 (2'-NCH_3), 41.9 (2-NCH_3), 38.1 (C-α'), 34.8 (C-1''), 29.4 (C-3''), 25.8 (C-4'), 23.5 (C-2''), 22.3 (C-4)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2926, 2854, 1656, 1578, 1507, 1352, 1262, 1203, 1114, 1012, 812

Purity (HPLC, method c) = 98%, d.r. > 99:1 (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{34}H_{42}N_2O_5 + H]^+$ 559.3166, found: 559.3172

(±)-*N*-Methyl-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (sc1)



$C_{27}H_{31}NO_4$

M_W = 433.23 g/mol

Carbamate **55** (100 mg, 0.175 mmol) was reduced following General Procedure 4. The reaction was completed after 4 h. Purification by flash column chromatography (2% triethylamine and 3% methanol in ethyl acetate, R_f = 0.29) affording the product as a beige solid.

yield: 49.3 mg, 0.114 mmol, 65%, beige solid

mp: 85.0 – 85.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.43 – 7.39 (m, 2H, 2''-H, 6''-H), 7.37 – 7.31 (m, 2H, 3''-H, 5''-H), 7.30 – 7.24 (m, 1H, 4''-H), 6.77 (d, *J* = 8.1 Hz, 1H, 5'-H), 6.66 (d, *J* = 2.0 Hz, 1H, 2'-H), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H, 6'-H), 6.54 (s, 1H, 5-H), 6.00 (s, 1H, 8-H), 5.07 (s, 2H, OC*H*$_2$-Ar), 3.85 (s, 3H, 4'-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.59 (dd, *J* = 7.6, 5.0 Hz, 1H, 1-H), 3.56 (s, 3H, 7-OCH_3), 3.15 – 3.09 (m, 2H, 3-H), 3.06 (dd, *J* = 13.7, 5.0 Hz, 1H, α-H), 2.83 – 2.76 (m, 1H, 4-H), 2.76 – 2.67 (m, 2H, α-H, 3-H), 2.54 (dt, *J* = 15.5, 4.7 Hz, 1H, 4-H), 2.48 (s, 3H, NCH_3)

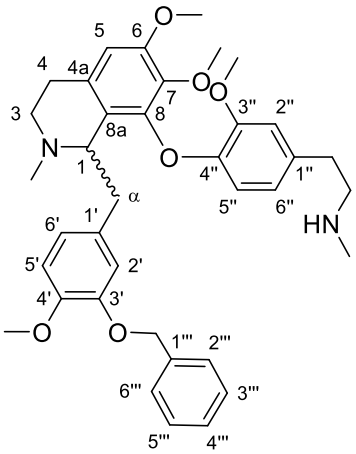
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 148.2 (C-4'), 147.8 (C-3'), 147.3 (C-6), 146.4 (C-7), 137.4 (C-1''), 132.6 (C-1'), 129.4 , 8a, 128.6 (C-3'', C-5''), 127.9 (C-4''), 127.4 (C-2'', C-6''), 126.2 (C-4a), 122.7 (C-6'), 116.0 (C-2'), 111.7 (C-5'), 111.2 (C-5), 111.1 (C-8), 71.2 (O*C*H$_2$-Ar), 64.9 (C-1), 56.2 (4'-OCH_3), 55.9 (6-OCH_3), 55.7 (7-OCH_3), 47.2 (C-3), 42.8 (NCH_3), 40.9 (C- α), 25.7 (C-4)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2938, 2826, 1606, 1510, 1374, 1223, 1135, 1013, 697

Purity (HPLC, method c) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{27}H_{31}NO_4 + H]^+$ 434.2326, found: 434.2322

(±)-8-(4-(2-((*N*-Methyl)amino)ethyl)-2-methoxyphenoxy)-*N*-methyl-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (sc2)



$C_{37}H_{44}N_2O_6$

M_W = 612.32 g/mol

Carbamate **58** (25.0 mg, 0.0343 mmol) was reduced following General Procedure 4. The reaction was completed after 4 h. Purification by flash column chromatography (ethyl acetate → 2% triethylamine and 5% methanol in ethyl acetate, R_f = 0.15) affording the product as a beige solid.

yield: 19.5 mg, 0.0318 mmol, 93%, pale orange solid

mp: 86.0 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.39 – 7.33 (m, 2H, 2'''-H, 6'''-H), 7.32 – 7.27 (m, 2H, 3'''-H, 5'''-H), 7.25 – 7.22 (m, 1H, 4'''-H), 6.83 (d, *J* = 2.0 Hz, 1H, 2''-H), 6.76 (d, *J* = 1.8 Hz, 1H, 2'-H), 6.72 (d, *J* = 8.1 Hz, 1H, 5'-H), 6.69 (dd, *J* = 8.2, 1.8 Hz, 1H, 6'-H), 6.59 (dd, *J* = 8.2, 2.0 Hz, 1H, 6''-H), 6.51 (s, 1H, 5-H), 6.46 (d, *J* = 8.2 Hz, 1H, 5''-H), 4.98 (dd, *J* = 15.5, 12.1 Hz, 2H, OC*H*$_2$-Ph), 3.90 (s, 3H, 3''-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.81 (s, 3H, 4'-OCH_3), 3.75 (dd, *J* = 9.6, 2.9 Hz, 1H, 1-H), 3.66 (s, 3H, 7-OCH_3), 3.21 (ddd, *J* = 13.3, 10.8, 5.2 Hz, 1H, 3-H), 2.96 – 2.87 (m, 5H, α-H, NCH_2-C*H*$_2$-Ar, NC*H*$_2$-CH_2-Ar), 2.86 – 2.82 (m, 1H, 4-H), 2.74 (dd, *J* = 14.3, 9.6 Hz, 1H, α-H), 2.69 (ddd, *J* = 13.3, 6.2, 2.4 Hz, 1H, 3-H), 2.48 (s, 3H, NCH_3), 2.39 (ddd, *J* = 16.8, 5.2, 2.5 Hz, 1H, 4-H), 2.17 (s, 3H, 2-NCH_3)

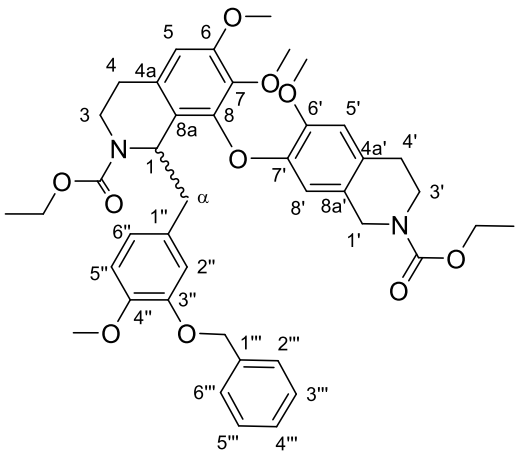
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 152.0 (C-6), 148.9 (C-3''), 147.8 (C-4'), 147.6 (C-3'), 146.5 (C-4''), 145.8 (C-8), 140.1 (C-7), 137.5 (C-1'''), 133.8 (C-1'), 132.3 (C-1''), 130.4 (C-4a), 128.6 (C-3''', C-5'''), 127.8 (C-4'''), 127.6 (C-2''', C-6'''), 124.6 (C-8a), 122.0 (C-6'), 120.8 (C-6''), 115.4 (C-2'), 114.4 (C-5''), 113.3 (C-2''), 111.5 (C-5'), 109.0 (C-5), 70.9 (O*C*H_2-Ph), 61.0 (7-OCH_3), 60.1 (C-1), 56.4 (3''-OCH_3), 56.1 (6-OCH_3), 56.1 (4'-OCH_3), 52.4 (N*C*H_2-CH_2-Ar), 44.5 (C-3), 42.3 (2-NCH_3), 40.2 (C-α), 35.1 (NCH_3), 34.4 (NCH_2-*C*H_2-Ar), 23.4 (C-4)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932, 2837, 1595, 1509, 1263, 1134, 1022, 806

Purity (HPLC, method c) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{37}H_{44}N_2O_6 + H]^+$ 613.3272, found: 613.3269

(±)-8-(*N*-Ethoxy-(6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxy-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (95)



$C_{42}H_{48}N_2O_{10}$

M_W = 740.33 g/mol

Carbamate **58** (118 mg, 0.162 mmol) and paraformaldehyde (10.0 mg, 0.330 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TFA as catalyst. The reaction was completed after 6 h. Purification by flash column chromatography (30% acetone in hexanes, R_f = 0.19) gave **95** as a white solid.

yield: 36.0 mg, 0.104 mmol, 47%, white solid

mp: 61.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.45 – 7.37 (m, 2H, 2'''-H, 6'''-H), 7.36 – 7.31 (m, 2H, 3'''-H, 5'''-H), 7.30 – 7.25 (m, 1H, 4'''-H), 6.73 (d, *J* = 8.2 Hz, 1H, 5''-H), 6.71 (s, 1H, 5'-H), 6.67 (d, *J* = 2.0 Hz, 1H, 2''-H), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H, 6''-H), 6.51 (s, 1H, 5-H), 6.34 (s, 1H, 8'-H), 5.36 (s, 1H, 1-H), 4.92 (s, 2H, OC*H*$_2$-Ar), 4.33 (s, 2H, 1'-H), 4.10 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$-CH_3), 4.06 – 3.93 (m, 1H, 3-H), 3.87 (s, 3H, 6'-OCH_3), 3.91 – 3.75 (m, 2H, OC*H*$_2$-CH_3), 3.82 (s, 3H, 6-OCH_3), 3.78 (s, 3H, 4''-OCH_3), 3.63 (s, 3H, 7-OCH_3), 3.60 (t, *J* = 6.0 Hz, 2H, 3'-H), 3.30 (ddd, *J* = 13.1, 10.0, 4.9 Hz, 1H, 3-H), 3.13 (dd, *J* = 14.0, 3.7 Hz, 1H, α-H), 2.80 (dd, *J* = 13.7, 9.1 Hz, 2H, α-H, 4-H), 2.74 (t, *J* = 6.0 Hz, 2H, 4'-H), 2.53 (d, *J* = 16.5 Hz, 1H, 4-H), 1.21 (t, *J* = 7.0 Hz, 3H, 'OCH_2-C*H*$_3$), 0.92 (br s, 3H, OCH_2-C*H*$_3$)

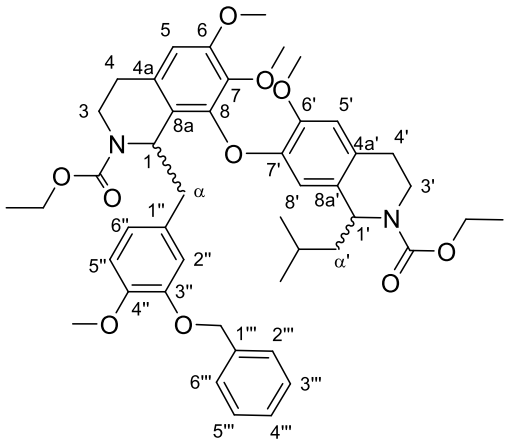
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.6 ('C=O), 155.4 (C=O), 152.6 (C-6), 149.0 (C-4''), 148.8 (C-3''), 148.2 (C-6'), 146.8 (C-7'), 145.3 (C-8), 140.6 (C-7), 137.9 (C-1'''), 132.3 (C-1''), 130.3 (C-4a), 128.5 (C-4a'), 128.4 (C-3''', C-5'''), 127.7 (C-4'''), 127.6 (C-2''', C-6'''), 126.0 (C-8a'), 124.2 (C-8a), 122.8 (C-6''), 117.3 (C-2''), 114.2 (C-5'), 113.6 (C-5''), 113.0 (C-8'), 109.8 (C-5), 71.8 (O*C*H_2-Ar), 61.3 ('O*C*H_2-CH_3), 60.9 (O*C*H_2-CH_3), 60.8 (7-OCH_3), 57.0, 56.8, 56.5 (6-OCH_3, 6'-O*C*H_3, 4''-OCH_3), 52.2 (C-1), 45.3 (C-1'), 41.6 (C-3'), 39.9 (C-α), 37.6 (C-3), 28.6 (C-4'), 28.1 (C-4), 14.7 ('OCH_2-*C*H_3), 14.3 (OCH_2-*C*H_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2838, 1689, 1510, 1422, 1218, 1111, 1020, 763

Purity (HPLC, method b) = 95% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{48}N_2O_{10} + H]^+$ 741.3382, found: 741.3378

(±)-8-(*N*-Ethoxy-(1-isobutyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-ethoxy-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (96)



$C_{46}H_{56}N_2O_{10}$

M_W = 796.39 g/mol

Carbamate **58** (50.0 mg, 0.0686 mmol) and 3-methylbutanal (10.0 µL, 0.0932 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TFA as catalyst. After 4 h an additional amount of 3-Methylbutanal (10.0 µL, 0.0932 mmol) were added. The reaction was completed after 12 h. Purification by flash column chromatography (10% ethyl acetate in dichloromethane, R_f = 0.27 (**sc4** precursor) and R_f = 0.24 (**sc5** precursor) gave the title compounds as a white solid.

sc4 precursor:

yield: 27.0 mg, 0.0339 mmol, 49%, white solid

mp 65.0 – 66.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.42 – 7.37 (m, 2H, 2'''-H, 6'''-H), 7.36 – 7.30 (m, 2H, 3'''-H, 5'''-H), 7.30 – 7.23 (m, 1H, 4'''-H), 6.73 (d, *J* = 8.1 Hz, 1H, 5''-H), 6.67 (d, *J* = 1.9 Hz, 1H, 2''-H), 6.66 (s, 1H, 5'-H), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H, 6''-H), 6.51 (s, 1H, 5-H), 6.29 (s, 1H, 8'-H), 5.33 (s, 1H, 1-H), 4.92 (s, 2H, OCH_2-Ar), 4.91 – 4.85 (m, 1H, 1'-H), 4.18 – 3.99 (m, 3H, 'OCH_2-CH_3, 3'-H), 4.00 – 3.89 (m, 1H, 3-H), 3.84 (s, 3H, 6'-OCH_3), 3.82 (s, 3H, 6-OCH_3), 3.78 (s, 3H, 4''-OCH_3), 3.81 – 3.72 (m, 2H, OCH_2-CH_3), 3.63 (s, 3H, 7-OCH_3), 3.32 (ddd, *J* = 13.1, 9.7, 4.9 Hz, 1H, 3-H), 3.20 (tt, *J* = 10.7, 4.6 Hz, 1H, 3'-H), 3.13 (dd, *J* = 14.0, 3.9 Hz, 1H, α-H), 2.89 – 2.78 (m, 2H, α-H, 4'-H), 2.79 – 2.71 (m, 1H, 4-H), 2.60 (dt, *J* = 16.1, 4.1 Hz, 1H, 4'-H), 2.51 (d, *J* = 15.9 Hz, 1H, 4-H), 1.60 (ddd, *J* = 13.9, 8.9, 5.4 Hz, 1H, α'-H), 1.56 – 1.48 (m, 1H, CH(CH_3)$_2$), 1.33 – 1.22 (m, 1H, α'-H), 1.20 (t, *J* = 7.1 Hz, 3H, 'OCH_2-CH_3), 0.93 (br s, 3H, OCH_2-CH_3), 0.85 (d, *J* = 6.4 Hz, 3H, CH(CH_3)$_2$), 0.81 (d, *J* = 6.5 Hz, 3H, CH(CH_3)$_2$)

^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.6 ('C=O), 155.4 (C=O), 152.7 (C-6), 149.0 (C-4''), 148.8 (C-3''), 148.1 (C-6'), 146.5 (C-7'), 145.6 (C-8), 140.8 (C-7), 137.9 (C-1'''), 132.4 (C-1''), 131.2 (C-8a'), 128.4 (C-3''', C-5'''), 127.9 (C-4a'), 127.7 (C-4'''), 127.6 (C-2''', C-6'''), 124.2 (C-8a), 122.9 (C-6''), 117.4 (C-2''), 114.2 (C-5'), 114.2 (C-8'), 113.6 (C-5''), 109.8 (C-5), 71.8

(O*C*H_2-Ar), 61.1 ('O*C*H_2-CH_3), 60.9 (O*C*H_2-CH_3), 60.8 (7-OCH_3), 56.9, 56.8, 56.6 (4''-OCH_3, 6'-OCH_3, 6-OCH_3), 52.8 (C-1'), 52.3 (C-1), 46.4 (C-α'), 40.1 (C-α), 37.8 (C-3, C-3'), 28.2 (C-4), 27.9 (C-4'), 25.0 (*C*H(CH_3)$_2$), 22.9, 22.5 (CH(*C*H_3)$_2$),14.6 ('OCH_2-CH_3), 14.4 (OCH_2-CH_3)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2836, 1689, 1509, 1423, 1256, 1109, 1023, 763

Purity (HPLC, method b) = 98% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for [$C_{46}H_{56}N_2O_{10}$ + H]$^+$ 797.4008, found: 797.4010

sc5 precursor:

yield: 27.0 mg, 0.0339 mmol, 49%, white solid

mp: 57.0 – 58.5 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.42 – 7.36 (m, 2H, 2'''-H, 6'''-H), 7.36 – 7.30 (m, 2H, 3'''-H, 5'''-H), 7.30 – 7.23 (m, 1H, 4'''-H), 6.73 (d, *J* = 8.1 Hz, 1H, 5''-H), 6.67 (s, 2H, 2''-H, 5'-H), 6.59 (dd, *J* = 8.1, 2.0 Hz, 1H, 6''-H), 6.50 (s, 1H, 5-H), 6.37 (s, 1H, 8'-H), 5.41 (s, 1H, 1-H), 4.92 (s, 2H, OC*H*$_2$-Ar), 4.90 (d, *J* = 5.3 Hz, 1H, 1'), 4.18 – 4.10 (m, 2H, 'OC*H*$_2$-CH_3), 4.09 – 3.94 (m, 2H, 3'-H, 3-H), 3.84 (s, 3H, 6'-OCH_3), 3.82 (s, 3H, 6-OCH_3), 3.90 – 3.71 (m, 2H, OC*H*$_2$-CH_3), 3.78 (s, 3H, 4''-OCH_3), 3.60 (s, 3H, 7-OCH_3), 3.29 (ddd, *J* = 13.2, 9.9, 4.9 Hz, 1H, 3-H), 3.21 (ddd, *J* = 13.6, 10.3, 4.6 Hz, 1H, 3'-H), 3.15 (dd, *J* = 14.0, 3.8 Hz, 1H, α-H), 2.90 – 2.74 (m, 3H, α-H, 4'-H, 4-H), 2.63 (dt, *J* = 16.1, 4.2 Hz, 1H, 4'-H), 2.50 (d, *J* = 16.0 Hz, 1H, 4-H), 1.67 – 1.48 (m, 2H, α'-H, C*H*(CH_3)$_2$), 1.33 – 1.22 (m, 1H, α'-H), 1.21 (t, *J* = 7.1 Hz, 3H, 'OCH_2-C*H*$_3$), 0.91 (br s, 3H, OCH_2-C*H*$_3$), 0.85 (d, *J* = 6.4 Hz, 3H, CH(C*H*$_3$)$_2$), 0.81 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$).

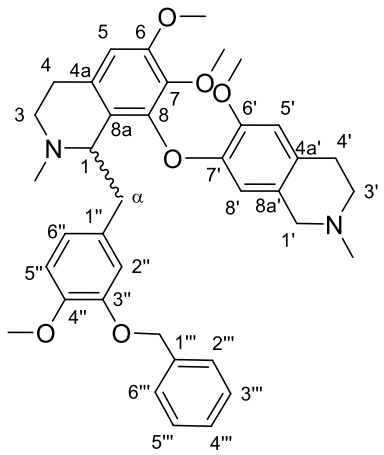
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.6 ('C=O), 155.5 (C=O), 152.6 (C-6), 149.0 (C-4''), 148.7 (C-3''), 148.2 (C-6'), 146.4 (C-7'), 145.5 (C-8), 140.7 (C-7), 137.9 (C-1'''), 132.3 (C-1''), 131.2 (C-8a'), 128.4 (C-3''', C-5'''), 128.0 (C-4a'), 127.7 (C-4'''), 127.6 (C-2''', C-6'''), 124.2 (C-8a), 122.9 (C-6''), 117.4 (C-2''), 114.4 (C-8'), 114.1 (C-5'), 113.6 (C-5''), 109.8 (C-5), 71.8 (O*C*H_2-Ar), 61.1 ('O*C*H_2-CH_3), 60.9 (O*C*H_2-CH_3), 60.7 (7-OCH_3), 56.8, 56.6 (4''-OCH_3, 6'-OCH_3, 6-OCH_3), 52.9 (C-1'), 52.1 (C-1), 46.4 (C-α'), 39.9 (C-α), 37.9 (C-3, C-3'), 28.0 (C-4), 28.0 (C-4'), 25.0 (*C*H(CH_3)$_2$), 23.0, 22.5 (CH(*C*H_3)$_2$), 14.6 ('OCH_2-*C*H_3), 14.3 (OCH_2-*C*H_3).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2922, 1692, 1511, 1424, 1256, 1112, 1023, 763

Purity (HPLC, method b) = 98% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for [$C_{46}H_{56}N_2O_{10}$ + H]$^+$ 797.4008, found: 797.4010

(±)-8-(*N*-Methyl-(6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-methyl-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (sc3)



$C_{38}H_{44}N_2O_6$

M_W = 624.32 g/mol

Carbamate **102** (60.0 mg, 0.0811 mmol) was reduced following General Procedure 4. The reaction was completed after 4 h. Purification by flash column chromatography (ethyl acetate → 1% triethylamine and 5% methanol in ethyl acetate, R_f = 0.24) affording the product as a white solid.

yield: 50.0 mg, 0.0800 mmol, 99%, white solid

mp: 47.5 – 48.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 – 7.35 (m, 2H, 2'''-H, 6'''-H), 7.34 – 7.29 (m, 2H, 3'''-H, 5'''-H), 7.28 – 7.23 (m, 1H, 4'''-H), 6.76 (d, *J* = 1.7 Hz, 1H, 2''-H), 6.72 (d, *J* = 8.1 Hz, 1H, 5''-H), 6.69 (dd, *J* = 8.1, 1.7 Hz, 1H, 6''-H), 6.67 (s, 1H, 5'-H), 6.52 (s, 1H, 5-H), 6.20 (s, 1H, 8'-H), 4.98 (q, *J* = 12.0 Hz, 2H, OC*H*$_2$-Ar), 3.86 (s, 3H, 6'-OCH_3), 3.85 (s, 3H, 6-OCH_3), 3.81 (s, 3H, 4''-OCH_3), 3.74 (dd, *J* = 9.8, 2.8 Hz, 1H, 1-H), 3.67 (s, 3H, 7-OCH_3), 3.32 (s, 2H, 1'-H), 3.25 (ddd, *J* = 13.2, 11.3, 5.1 Hz, 1H, 3-H), 2.91 (dd, *J* = 14.3, 2.7 Hz, 1H, α-H), 2.92 – 2.84 (m, 1H, 4-H), 2.82 (t, *J* = 6.0 Hz, 2H, 4'-H), 2.79 – 2.64 (m, 3H, α-H, 3-H), 2.61 (t, *J* = 5.8 Hz, 2H, 3'-H), 2.45 – 2.37 (m, 1H, 4-H), 2.36 (s, 3H, 2'-NCH_3), 2.16 (s, 3H, 2-NCH_3)

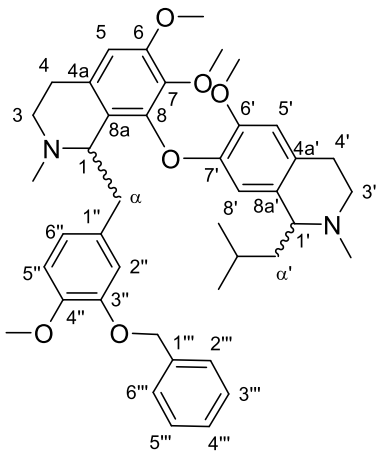
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 152.0 (C-6), 147.8 (C-4''), 147.7 (C-3''), 147.4 (C-6'), 145.9 (C-7'), 145.8 (C-8), 140.3 (C-7), 137.6 (C-1'''), 134.0 (C-1''), 130.3 (C-4a), 128.5 (C-3''', C-5'''), 127.8 (C-4'''), 127.7 (C-2''', C-6'''), 127.1 (C-4a'), 126.9 (C-8a'), 124.9 (C-8a), 122.0 (C-6''), 115.4 (C-2''), 112.8 (C-5'), 111.9 (C-8'), 111.6 (C-5''), 109.0 (C-5), 70.9 (O*C*H$_2$-Ar), 60.9 (7-O*C*H_3), 60.1 (C-1), 57.5 (C-1'), 56.4 (6'-OCH_3), 56.2 (4''-OCH_3 or 6-OCH_3), 56.1 (4''-OCH_3 or 6-OCH_3), 53.0 (C-3'), 46.1 (2'-NCH_3), 44.4 (C-3), 42.3 (2-NCH_3), 40.2 (C-α), 29.0 (C-4'), 23.4 (C-4).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932, 2836, 1605, 1511, 1450, 1258, 1219, 1112, 1010, 797

Purity (HPLC, method c) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{38}H_{44}N_2O_6 + H]^+$ 625.3272, found: 625.3263

(±)-8-(*N*-Methyl-(1-isobutyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-*N*-methyl-6,7-dimethoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (sc4-sc5)



$C_{42}H_{52}N_2O_6$

M_W = 680.38 g/mol

Carbamate **96** (**sc4** precursor: 25.0 mg, 0.0314 mmol and **sc5** precursor: 22.0 mg, 0.0276 mmol), was reduced following General Procedure 4. The reaction was completed after 4 h. Purification by flash column chromatography (ethyl acetate → 0.5% triethylamine and 5% methanol in ethyl acetate, R_f = 0.13) affording the products as a white solid.

sc4:

yield: 17.2 mg, 0.0253 mmol, 80%, white solid

mp: 46.5 – 48.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.38 (d, *J* = 7.2 Hz, 2H, 2'''-H, 6'''-H), 7.36 – 7.22 (m, 3H, 3'''-H, 4'''-H, 5'''-H), 6.78 (d, *J* = 1.6 Hz, 1H, 2''-H), 6.74 (d, *J* = 8.1 Hz, 1H, 5''-H), 6.71 (dd, *J* = 8.5, 1.2 Hz, 1H, 6''-H), 6.63 (s, 1H, 5'-H), 6.53 (s, 1H, 5-H), 6.25 (s, 1H, 8'-H), 5.00 (q, 2H, O*C*H_2-Ar), 3.86 (s, 3H, 6'-OCH_3), 3.85 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 4''-OCH_3), 3.79 (d, *J* = 11.1 Hz, 1H, 1-H), 3.66 (s, 3H, 7-OCH_3), 3.30 – 3.21 (m, 2H, 1'-H, 3-H), 3.16 – 3.06 (m, 1H, 3'-H), 2.97 – 2.67 (m, 6H, α-H, 3'-H, 3-H, 4'-H, 4-H), 2.57 – 2.48 (m, 1H, 4'-H), 2.42 (dd, *J* = 18.0, 3.7 Hz, 1H, 4-H), 2.36 (s, 3H, 2'-NCH_3), 2.18 (s, 3H, 2-NCH_3), 1.65 (dq, *J* = 13.2, 6.7 Hz, 1H, C*H*$(CH_3)_2$), 1.52 (dt, *J* = 13.8, 6.9 Hz, 1H, α'-H), 1.19 (ddd, *J* = 13.8, 8.1, 5.4 Hz, 1H, α'-H), 0.79 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3)_2$), 0.75 (d, *J* = 6.7 Hz, 3H, CH(C*H*$_3)_2$)

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 152.0 (C-6), 147.8 (C-3''), 147.7 (C-4''), 147.2 (C-6'), 146.0 (C-8), 145.9 (C-7'), 140.3 (C-7), 137.6 (C-1'''), 134.0 (C-1''), 131.1 (C-8a'), 130.2 (C-4a), 128.5 (C-3''',C- 5'''), 127.8 (C-4'''), 127.7 (C-2''',C-6'''), 127.1 (C-4a'), 124.8 (C-8a), 122.0 (C-6''), 115.4 (C-2''), 113.6 (C-8'), 112.8 (C-5'), 111.6 (C-5''), 109.1 (C-5), 70.9 (O*C*H_2-Ar), 60.9 (7-OCH_3), 60.8 (C-1'), 60.1 (C-1), 56.3 (4''-OCH_3, 6'-OCH_3 or 6-OCH_3), 56.2 (4''-OCH_3, 6'-OCH_3 or 6-OCH_3), 56.1 (4''-OCH_3, 6'-OCH_3 or 6-OCH_3), 46.1 (C-3'), 45.1 (C-α'), 44.4 (C-3), 42.3 (2-

NCH_3), 42.1 (2'-NCH_3), 40.2 (C-α), 25.2 ($CH(CH_3)_2$), 23.9 (C-4'), 23.4 (C-4), 23.2 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2840, 1606, 1508, 1454, 1259, 1113, 1013, 762, 696

Purity (HPLC, method c) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{52}N_2O_6 + H]^+$ 681.3898, found: 681.3891

sc5:

yield: 15.3 mg, 0.0225 mmol, 81%, white solid

mp: 71.0 – 72.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 (d, *J* = 7.0 Hz, 2H, 2'''-H, 6'''-H), 7.35 – 7.23 (m, 3H, 3'''-H, 4'''-H, 5'''-H), 6.77 (d, *J* = 23.5 Hz, 3H, 2''-H, 5''-H, 6''-H), 6.63 (s, 1H, 5'-H), 6.53 (s, 1H, 5-H), 6.18 (s, 1H, 8'-H), 4.98 (q, *J* = 12.0 Hz, 2H, OCH_2-Ar), 3.87 (s, 3H, 6'-OCH_3), 3.86 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 4''-OCH_3), 3.71 (s, 3H, 7-OCH_3), 3.67 (dd, *J* = 9.6, 2.9 Hz, 1H, 1-H), 3.34 – 3.21 (m, 2H, 1'-H, 3-H), 3.12 (ddd, *J* = 13.7, 9.6, 5.2 Hz, 1H, 3'-H), 2.99 (dd, *J* = 14.3, 2.8 Hz, 1H, α-H), 2.92 – 2.68 (m, 5H, α-H, 3-H, 3'-H, 4-H, 4'-H), 2.52 – 2.36 (m, 2H, 4-H, 4'-H), 2.36 (s, 3H, 2-'NCH_3), 2.18 (s, 3H, 2-NCH_3), 1.69 (dt, *J* = 13.7, 7.0 Hz, 1H, C$H(CH_3)_2$), 1.54 (ddd, *J* = 14.0, 8.3, 5.5 Hz, 1H, α'-H), 1.15 (ddd, *J* = 13.8, 8.6, 5.0 Hz, 1H, α'-H), 0.79 (d, *J* = 6.5 Hz, 3H, $CH(CH_3)_2$), 0.76 (d, *J* = 6.6 Hz, 3H, $CH(CH_3)_2$)

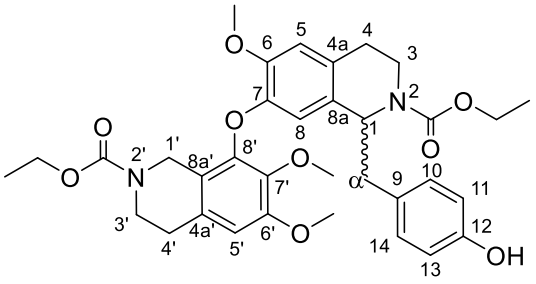
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 152.0 (C-6), 147.8 (C-4''), 147.7 (C-3''), 147.1 (C-6'), 145.9 (C-7'), 140.4 (C-7), 137.6 (C-1'''), 134.0 (C-1''), 131.3 (C-8a'), 130.4 (C-4a), 128.5 (C-3''', C-5'''), 127.8 (C-4'''), 127.7 (C-2''', C-6'''), 127.0 (C-4a'), 124.7 (C-8a), 122.1 (C-2'' or 6''), 115.5 (C-2'' or 6''), 113.2 (C-8'), 112.8 (C-5'), 111.5 (C-5''), 109.1 (C-5), 70.9 (OCH_2-Ar), 61.0 (7-OCH_3), 60.6 (C-1'), 60.4 (C-1), 56.3 (4''-OCH_3, 6'-OCH_3 or 6-OCH_3), 56.1 (4''-OCH_3, 6'-OCH_3 or 6-OCH_3), 45.7 (C-3'), 45.7 (C-α'), 44.6 (C-3), 42.4 (2-NCH_3), 42.1 (2'-NCH_3), 40.5 (C-α), 25.2 ($CH(CH_3)_2$), 23.5 (C-4'), 23.4 ($CH(CH_3)_2$), 23.2 (C-4), 22.4 ($CH(CH_3)_2$). The resonance of C-8 could not be identified.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2835, 1606, 1508, 1451, 1257, 1216, 1113, 1013, 752

Purity (HPLC, method c) = 94% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{42}H_{52}N_2O_6 + H]^+$ 681.3898, found: 681.3895

***N*,*N'*-Bisnor-Muraricine bis(ethylcarbamate) (97)**



$C_{34}H_{40}N_2O_9$

M_w = 620.27 g/mol

Intermediate **66** (53.0 mg, 0.0871 mmol) and paraformaldehyde (5.2 mg, 0.174 mmol) were condensed following General Procedure 2 (*inter*molecular *N*-acyl Pictet-Spengler reaction) using TFA as catalyst. The reaction was completed after 2 h. Purification by flash column chromatography (20% ethyl acetate in dichloromethane, R_f = 0.14) gave the title compound as a white solid.

yield: 36.8 mg, 0.0593 mmol, 68%, white solid

mp: 91.0 – 93.0 °C

^{1}H NMR (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.80 – 6.75 (m, 2H, 10-H, 14-H), 6.68 (s, 1H, 5-H), 6.61 – 6.57 (m, 2H, 11-H, 13-H), 6.51 (s, 1H, 5'-H), 6.03 (s, 1H, 8-H), 4.95 (t, *J* = 6.6 Hz, 1H, 1-H), 4.41 (d, *J* = 17.1 Hz, 1H, 1'-H), 4.29 (d, *J* = 17.1 Hz, 1H, 1'-H), 4.13 (q, *J* = 7.1 Hz, 2H, 'OC*H*$_2$CH$_3$), 4.04 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.87 (s, 3H, 6-OCH$_3$), 3.88 – 3.82 (m, 1H, 3-H), 3.82 (s, 3H, 6'-OCH$_3$), 3.62 – 3.57 (m, 1H, 3'-H), 3.59 (s, 3H, 7'-OCH$_3$), 3.34 – 3.25 (m, 1H, 3-H), 2.91 (dd, *J* = 13.6, 6.0 Hz, 1H, α-H), 2.79 – 2.72 (m, 4H, α-H, 4'-H, 4-H), 2.61 (dt, *J* = 16.0, 5.2 Hz, 1H, 4-H), 1.23 (t, *J* = 7.1 Hz, 3H, 'OCH$_2$C*H*$_3$), 1.17 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$)

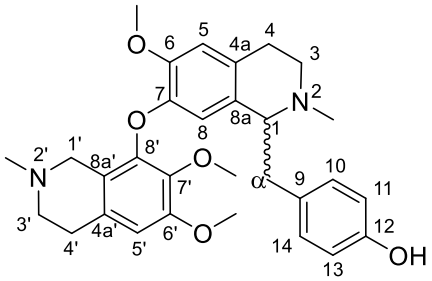
^{13}C NMR (101 MHz, Tcl_2, 100 °C) δ [ppm] = 156.0 ('C=O), 155.5 (C=O), 154.4 (C-12), 152.4 (C-6'), 148.5 (C-6), 146.2 (C-7), 145.9 (C-8'), 140.6 (C-7'), 130.6 (C-10, C-14), 130.4 (C-9), 130.2 (C-4a'), 129.3 (C-8a), 128.6 (C-4a), 120.2 (C-8a'), 115.4 (C-11, C-13), 114.9 (C-8), 113.9 (C-5), 109.8 (C-5'), 61.4 ('O*C*H$_2$CH$_3$), 61.2 (O*C*H$_2$CH$_3$), 60.7 (7'-OCH$_3$), 56.9 (6-OCH$_3$), 56.6 (6'-OCH$_3$), 56.3 (C-1), 42.3 (C-α), 41.5 (C-1'), 41.5 (C-3'), 39.1 (C-3), 28.9 (C-4'), 4', 28.2 (C-4), 14.7 ('OCH$_2$*C*H$_3$), 14.7 (OCH$_2$*C*H$_3$)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2855, 1670, 1612, 1513, 1425, 1236, 1108, 1023, 823, 769

Purity (HPLC, method b) = 76% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{34}H_{40}N_2O_9 + H]^+$ 621.2807, found: 621.2806

Racemic muraricine (*rac*-34)



$C_{30}H_{36}N_2O_5$

M_w = 504.26 g/mol

Muraricincarbamate **97** (35.0 mg, 0.0564 mmol) was reduced following General Procedure 4. The reaction was completed after 3 h. Purification by flash column chromatography (10% methanol and 2% triethylamine in ethyl acetate, R_f = 0.22) gave the title compound as a beige solid.

yield: 8.0 mg, 0.0158 mmol, 23%, beige solid

mp: 63.0 – 65.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.66 (s, 1H, 5-H), 6.60 (d, J = 8.0 Hz, 2H, 10-H, 14-H), 6.53 (d, J = 8.0 Hz, 2H, 11-H, 13-H), 6.47 (s, 1H, 5'-H), 4.83 (s, 1H, 8-H), 3.89 (s, 3H, 6-OCH_3), 3.80 (s, 3H, 6'-OCH_3), 3.83 – 3.76 (m, 1H, 1'-H), 3.58 (dd, J = 10.5, 3.0 Hz, 1H, 1-H), 3.39 (s, 3H, 7'-OCH_3), 3.41 – 3.31 (m, 3H, α-H, 3-H, 4'-H), 3.29 – 3.22 (m, 1H, 1'-H), 3.12 (dd, J = 11.0, 5.4 Hz, 1H, 3'-H), 3.03 – 2.93 (m, 2H, 3-H, 4-H), 2.87 – 2.75 (m, 1H, 4-H), 2.70 (d, J = 16.6 Hz, 1H, 4'-H), 2.62 (s, 3H, 2-NCH_3), 2.61 (s, 3H, 2'-NCH_3), 2.53 (t, J = 11.8 Hz, 1H, α-H), 2.47 – 2.38 (m, 1H, 3'-H)

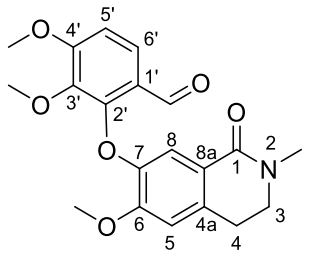
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.4 (C-12), 152.1 (C-6'), 147.6 (C-6), 144.2 (C-7), 144.1 (C-8'), 138.9 (C-7'), 130.9 (C-10, C-14), 129.7 (C-9), 129.0 (C-4a'), 126.1 (C-8a), 125.6 (C-4a), 118.8 (C-8a'), 118.3 (C-11, C-13), 115.1 (C-8), 111.9 (C-5), 108.2 (C-5'), 65.2 (C-1), 60.2 (7'-OCH_3), 56.2 (6-OCH_3), 56.1 (6'-OCH_3), 53.0 (C-1'), 52.4 (C-3'), 45.6 (2'-NCH_3), 45.5 (C-3), 41.8 (2-NCH_3), 39.6 (C-α), 28.2 (C-4'), 24.6 (C-4). The NMR data are mainly in accordance with literature[119].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2850, 1611, 1512, 1453, 1259, 1118, 1064, 834, 796

Purity (HPLC, method c) = > 99% (λ = 210 nm)

HRMS (ESI): *m/z* calcd for $[C_{30}H_{36}N_2O_5 + H]^+$ 505.2697, found: 505.2697

3,4-Dimethoxy-2-((6-methoxy-2-methyl-3,4-dihydroisoquinolin-1(*2H*)-one-7-yl)oxy)benzaldehyde (99)



$C_{20}H_{21}NO_6$

M_w = 371.14 g/mol

Thalifoline **47** (0.368 g, 1.77 mmol) and 2-bromo-3,4-dimethoxybenzaldehyde (**48**, 0.435 g, 1.77 mmol) were reacted following General Procedure 3 (*inter*molecular Ullmann coupling). The reaction was completed after 48 h. The crude product was purified by flash column chromatography (40% EtOAc in dichloromethane, R_f = 0.22), yielding the desired product (**99**) as a light yellow solid.

yield: 0.323 g, 0.87 mmol, 49%, light yellow solid

mp: 129.0 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 10.10 (d, J = 0.9 Hz, 1H, CHO), 7.70 (d, J = 8.9 Hz, 1H, 6'-H), 7.31 (s, 1H, 8-H), 6.87 (d, J = 8.8 Hz, 1H, 5'-H), 6.74 (s, 1H, 5-H), 3.98 (s, 3H, 6-OCH_3), 3.94 (s, 3H, 4'-OCH_3), 3.69 (s, 3H, 3'-OCH_3), 3.51 (t, J = 6.7 Hz, 2H, 3-H), 3.06 (s, 3H, NCH_3), 2.95 (t, J = 6.7 Hz, 2H, 4-H)

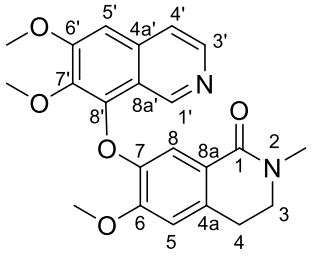
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 188.2 (CHO), 164.2 (C-1), 159.4 (C-4'), 151.7 (C-6), 151.6 (C-2'), 147.6 (C-7), 141.4 (C-3'), 133.7 (C-4a), 124.4 (C-6'), 123.4 (C-1'), 122.2 (C-8a), 115.0 (C-8), 110.3 (C-5), 109.0 (C-5'), 60.9 (3'-OCH_3), 56.3, 56.2 (4-'OCH_3, 6-OCH_3), 48.2 (C-3), 35.0 (NCH_3), 27.7 (C-4)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932, 2852, 1677, 1643, 1588, 1495, 1454, 1180, 1110, 1020, 819, 773

Purity (HPLC, method c) = 90% (λ = 210 nm)

HRMS (ESI): *m/z* = calcd. for $[C_{20}H_{21}NO_6 + H]^+$ 372.1442, found: 372.1439

Berbanine (35)



$C_{22}H_{22}N_2O_5$

M_w = 394.15 g/mol

Diaryl ether **99** (0.150 g, 0.404 mmol) and aminoacetaldehyde dimethyl acetal (48.4 µL, 0.444 mmol) were dissolved in anhydrous toluene (5.0 mL) and a small number of molecular sieves 4 Å was added. The mixture was heated at 100 °C for 4 h under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered to remove the molecular sieves and the solvent was evaporated *in vacuo*. The oily residue was suspended in trifluoroacetic anhydride (TFAA, 5.0 mL) at 0 °C and added dropwise to a mixture of boron trifluoride acetic acid complex (112 µL, 0.808 mmol) in 2.0 mL TFAA at 0 °C. The reaction mixture was allowed to warm up to ambient temperature and stirred for 18 h. The mixture was poured into ice-water, basified with 25% aqueous NH_3 (pH 12-14) and extracted with $CHCl_3$ (3 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% MeOH and 2% NEt_3 in EtOAc, R_f = 0.17) to give the title compound as a white solid.

yield: 75.2 mg, 0.191 mmol, 47%, white solid

mp: 126.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.16 (s, 1H, 1'-H), 8.40 (d, *J* = 5.7 Hz, 1H, 3'-H), 7.50 (d, *J* = 5.7 Hz, 1H, 4'-H), 7.20 (s, 1H, 8-H), 6.99 (s, 1H, 5'-H), 6.78 (s, 1H, 5-H), 4.04 (s, 3H, 6-OCH_3), 4.01 (s, 3H, 6'-OCH_3), 3.85 (s, 3H, 7'-OCH_3), 3.49 (t, J = 6.9 Hz, 2H, 3-H), 3.01 (s, 3H, NCH_3), 2.95 (t, *J* = 6.7 Hz, 2H, 4-H)

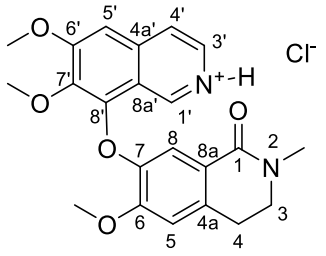
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 164.3 (C-1), 156.9 (C-6'), 151.8 (C-6), 147.5 (C-7), 146.7 (C-1'), 143.4 (C-3'), 143.0 (C-8'), 142.1 (C-7'), 134.0 (C-4a'), 133.7 (C-4a), 122.3 (C-8a), 119.6 (C-8a'), 119.3 (C-4'), 114.9 (C-8), 110.4 (C-5), 102.7 (C-5'), 61.3 (7'-OCH_3), 56.5 (6-OCH_3), 56.2 (6'-OCH_3), 48.3 (C-3), 35.1 (NCH_3), 27.8 (C-4)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2934, 2848, 1736, 1691, 1642, 1604, 1492, 1471, 1333, 1252, 1183, 1114, 1014, 849, 773

Purity (HPLC, method c) = 96% (λ = 210 nm)

HRMS (ESI): *m/z* = calcd. for $C_{22}H_{22}N_2O_5$ $[M+H]^+$ 395.1602, found: 395.1596

Berbanine ·HCl (35 ·HCl)



$C_{22}H_{23}ClN_2O_5$

M_w = 430.13 g/mol

Berbanine (**35**, 23.0 mg, 0.0583 mmol) was dissolved in 2 mL 1,4-dioxane and treated with an excess of HCl (4.0 M in 1,4-dioxane). The resulting precipitate was vacuum filtered over a Buchner funnel and washed with diethyl ether. The desired product was obtained as a yellow solid.

yield: 23.3 mg, 0.0542 mmol, 93%, yellow solid

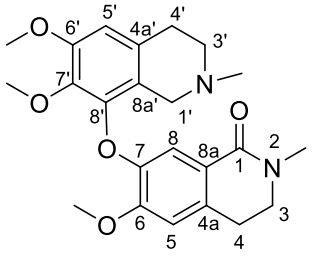
mp: 186.0 – 188.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.22 (d, J = 5.3 Hz, 1H, 1'-H), 8.32 (br s, 1H, 3'-H), 7.96 (d, J = 6.2 Hz, 1H, 4'-H), 7.20 (s, 1H, 5'-H), 7.19 (s, 1H, 8-H), 6.81 (s, 1H, 5-H), 4.13 (s, 3H, 6'-OCH_3), 4.01 (s, 3H, 6-OCH_3), 3.93 (s, 3H, 7'-OCH_3), 3.54 (t, J = 6.7 Hz, 2H, 3-H), 3.04 (s, 3H, NCH_3), 2.98 (t, J = 6.8 Hz, 2H, 4-H)

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 164.0 (C-1), 162.1 (C-6'), 151.7 (C-6), 146.3 (C-7), 145.0 (C-7'), 143.5 (C-8'), 139.4 (C-1'), 137.1 (C-4a'), 135.1 (C-4a), 131.1 (C-3'), 122.7 (C-4'), 122.3 (C-8a), 119.5 (C-8a'), 114.8 (C-8), 110.9 (C-5), 103.0 (C-5'), 61.5 (7'-OCH_3), 57.2 (6'-OCH_3), 56.5 (6-OCH_3), 48.2 (C-3), 35.2 (NCH_3), 27.8 (C-4)

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3390, 2923, 2622, 2064, 1605, 1477, 1397, 1257, 1179, 1116, 1016, 851, 772

Berbidine (**36**)



$C_{23}H_{28}N_2O_5$
M_w = 412.20 g/mol

Berbanine (**35**, 0.040 g, 0.101 mmol) was dissolved in acetone (1.0 mL) and iodomethane (63 µL, 1.01 mmol, 10 eq.) was added. The mixture was stirred at 45 °C for 3.5 h. After cooling to room temperature, the volatiles were removed *in vacuo*. The obtained methiodide was dissolved in 1.5 mL of a mixture of 4% water in MeOH (vol %)), the mixture cooled to 0 °C and sodium borohydride (19.2 mg, 0.507 mmol, 5 eq.) was added in portions. The reaction was stirred for 1 h, while it was allowed to warm to room temperature. The solvent was removed *in vacuo*, the residue quenched with water (20 mL) which was basified with a 2M NaOH solution (pH 12-14). The aqueous phase was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (5% MeOH and 2% NEt_3 in EtOAc → 7.5% MeOH and 2% NEt_3 in EtOAc, R_f = 0.28) yielded berbidine (**36**) as a white solid.

yield: 36.5 mg, 0.089 mmol, 88%, white solid

mp: 113.0 °C (ref.[158]: 128 - 130 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.23 (s, 1H, 8-H), 6.71 (s, 1H, 5-H), 6.53 (s, 1H, 5'-H), 3.98 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 6'-OCH_3), 3.64 (s, 3H, 7'-OCH_3), 3.50 (t, J = 6.7 Hz, 2H, 3-H), 3.45 (s, 2H, 1'-H), 3.05 (s, 3H, 2-NCH_3), 2.93 (t, J = 6.7 Hz, 2H, 4-H), 2.87 (t, J = 6.0 Hz, 2H, 4'-H), 2.66 (t, J = 6.0 Hz, 2H, 3'-H), 2.38 (s, 3H, 2'-NCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 164.5 (C-1), 152.1 (C-6'), 151.7 (C-6), 146.9 (C-7), 144.8 (C-8'), 139.8 (C-7'), 132.8 (C-4a), 129.9 (C-4a'), 122.3 (C-8a), 121.2 (C-8a'), 114.1 (C-8), 110.3 (C-5), 109.4 (C-5'), 61.0 (7'-OCH_3), 56.4 (6-OCH_3), 56.1 (6'-OCH_3), 52.4 (C-3'), 52.3 (C-1'), 48.4 (C-3), 45.9 (2'-NCH_3, 35.1 (2-NCH_3), 29.1 (C-4'), 27.8 (C-4). The NMR data are mainly in accordance with literature[159-161].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 2837, 1733, 1643, 1604, 1495, 1451, 1339, 1280, 1186, 1116, 1070, 1013, 815, 774

Purity (HPLC, method c) = 97% (λ = 210 nm)

HRMS (ESI): *m/z* = calcd. for $[C_{23}H_{28}N_2O_5 + H]^+$ 413.2071, found: 413.2064

7 APPENDIX

7.1 SUPPLEMENTARY MATERIAL

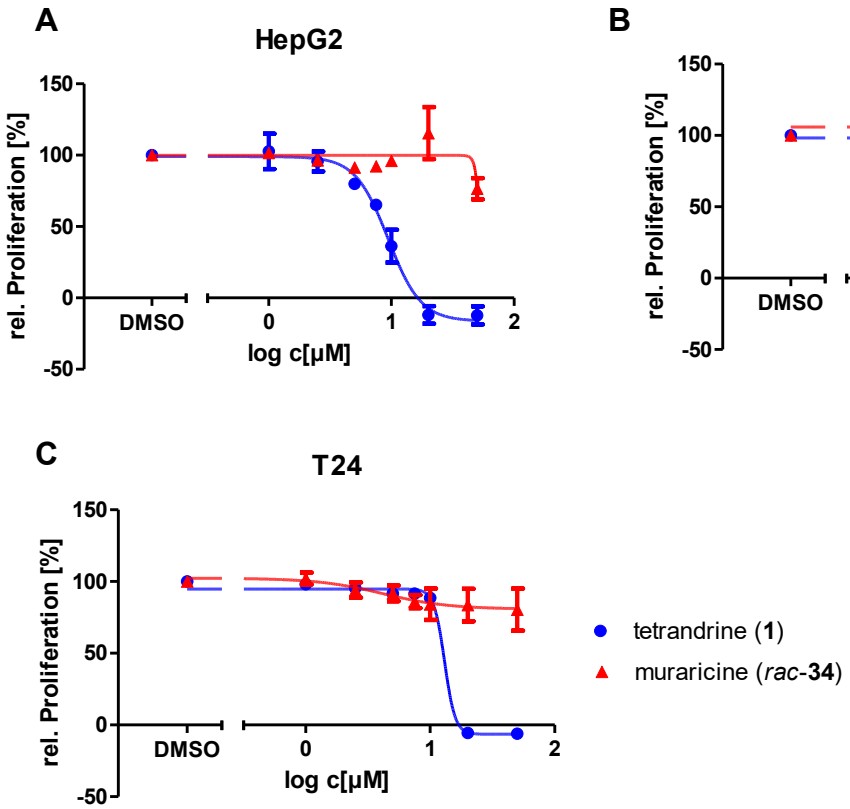


Figure 22. Antiproliferative effects of racemic muraricine (*rac*-**34**) and tetrandrine (**1**) on hepatocellular carcinoma (HepG2, **A**), colorectal adenocarcinoma (HCT-15, **B**) and bladder carcinoma (T24, **C**) cell lines. Proliferation is shown as percentage of vehicle control after subtraction of the zero value. Line graphs display mean ± SEM of three independent experiments.

7.2 ABBREVIATIONS

Å	Ångström
APCI	atmospheric pressure chemical ionziation
ASAP	atmospheric pressure solids analysis probe
ATR	attenuated total reflectance
Bn	benzyl
calcd	calculated
COSY	homonuclear correlation spectroscopy
CoV	coronavirus
CTB	cell titer blue
DCM	dichloromethane
δ	chemical shift in ppm
DEPT	distortionless enhancement by polarization transfer
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EI	electron ionization
eq.	equivalent
ESI	electron spray ionization
EtOAc	ethylacetate
EtOH	ethanol
FCC	flash column chromatography
GC	gas chromatography
h	hour
HepaRG	hepatic stem cells
HepG2	human hepatocellular carcinoma cells
HMBC	heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple-quantum correlation
HPLC	high performance liquid chromatography
HSQC	heteronuclear single quantum correlation
HR	high resolution
HUVEC	human umbilical vein endothelial cells
Hz	Hertz
IC_{50}	inhibitory concentration
IR	infrared
J	coupling constant
λ	wave length

LDA	Lithiumdiisopropylamid
MERS	middle eastern respiratory syndrome
MeOH	methanol
(m)mol	(milli)mole
mp	melting point
MS	mass spectrometry
M_w	molecular weight
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PBMC	peripheral blood mononuclear cells
P-gp	P-glycoprotein
p-TsOH	*para*-toluolsulfonic acid
R_f	retardation factor
rt	room temperature
SARS	severe acute respiratory syndrome
Tcl_2	deuterated tetrachloroethane
TFA	trifluoroacetic acid
TFE	trifluoroethanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TPC	two pore channel
VCR	vincristine
VCR-R CEM	vincristine-resistant acute lymphoblastic leukemia cells

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